UNIVERSITÉ DU QUÉBEC À MONTRÉAL

RÉACTIONS DE *N*–, *O*–, *S*–ARYLATION CATALYSÉES AU CUIVRE IMPLIQUANT DES ORGANOBISMUTHINES FONCTIONNALISÉS ET APPLICATION À L'ARYLATION D'ACIDES AMINÉS ET DE PEPTIDES

MÉMOIRE

COMME EXIGENCE PARTIELLE

DE LA MAÎTRISE EN CHIMIE

PRÉSENTÉ PAR

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AVANT-PROPOS

La présente recherche a été effectuée sous la direction du professeur Alexandre Gagnon qui a débuté sa carrière à l'UQÀM en 2011. Ses intérêts de recherche comprennent la chimie médicinale, la chimie organique, ainsi que la chimie organométallique et plus particulièrement la chimie du bismuth. Depuis l'année 2007, durant ses diverses expériences, il a pu développer de nombreuses méthodes d'alkylation et d'arylation catalysées au cuivre ou au palladium à base de trialkylbismuthines et de triarylbismuthines.

En outre, le groupe Gagnon a développé des méthodologies de dérivatisation de groupes fonctionnels directement sur les triarylbismuthines menant ainsi à des fonctionnalités plus élaborées et utiles en synthèse organique et en chimie médicinale.

En ce qui concerne les méthodologies développées par catalyse au cuivre, le groupe Gagnon a développé une méthode pour effectuer la *N*-cyclopropylation directe d'amides et d'hétérocycles azotés (indoles, pyrroles, etc.) en utilisant le tricyclopropylbismuth. Par la suite, les triarylbismuthines ont été employés pour aryler des phénols, des aminoalcools, ainsi que des hétérocycles azotés.

Concernant les réactions catalysées au palladium, le groupe Gagnon a développé des méthodes pour transférer des aryles hautements fonctionnalisés et des groupements alkyles sur des halogénures (ou pseudohalogénures tels que des triflates) d'aryles et d'hétéroaryles.

Compte tenu des méthodologies développées par le professeur Gagnon, soit l'arylation de substrats tels que des indoles (présent dans le tryptophane), des imidazoles (présent dans l'histidine), des phénols (présent dans la tyrosine) et des aminoalcools (présent dans la sérine et la thréonine), celles-ci ont été transposées à l'arylation des chaînes latérales d'acides aminés.

La contribution de la présente recherche servira à approfondir nos connaissances sur la modification des chaînes latérales d'acides aminés, en particulier la tyrosine, en employant des triarylbismuthines, ce qui n'a jusqu'à présent pas été rapporté dans la littérature. Ce travail a comme but de développer une méthode chimiosélective qui nous permettrait de marquer un résidu d'acide aminé spécifique pour être en mesure de suivre ces peptides à travers des processus biochimiques.

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LISTE D'ABRÉVIATIONS ET ACRONYMES

1° : Primaire

2° : Secondaire

3° : Tertiaire

(br) : Large (broad)

(l) : État liquide

[O] : Oxydant/Oxydation

Ac : Acétyle

acac : Acétylacétonate

AcO/OAc : Acétate

AcOEt/EtOAc : Acétate d'éthyle (Ethyl acetate)

AcOH : Acide acétique

Ala : Alanine

All : Allyle

Ar : Aryle

Asn : Aspargine

Asp : Acide aspartique

$BiAr_3$: Triarylbismuthine

BINAP : 2,2'Bis(diphénylphosphino)-1,1'-binaphtalène

BiR_3 : Trialkylbismuthine

Bn : Benzyle

Boc: *Tert*-butyloxycarbonyle

Bzl/Bz : Benzoyle

Bu : Butyle

CCM/TLC : Chromatographie sur couche mince (Thin layer chromatography)

Cbz : Carboxybenzyle

cPr : Cyclopropyle

Cy : Cyclohexyle

Cys : Cystéine

d : Doublet

dba : Dibenzylidèneacétone

DCM : Dichlorométhane

DCE : 1,2-Dichloroéthane

dd : Doublet de doublet

ddd : doublet de doublet de doublet

dhAla : Déhydroalanine

DiPEA : *N,N*-diisopropyléthylamine

DMA : *N,N*-Diméthylacétamide

DMAP : 4-(Diméthylamino)pyridine

DME : Diméthoxyéthane

DMF: *N,N*-Diméthylformamide

dppf : 1,1'-Bis(diphénylphosphino)ferrocène

dq : Doublet de quadruplet

dt : Doublet de triplet

Éq(s) : Équation(s)

éq/équiv/eq/equiv : Équivalent

Et : Éthyle

Et_2O : Éther diéthylique

Et_3N : Triéthylamine

Fmoc : Fluorénylméthoxycarbonyle

GF/FG: Groupe fonctionnel (Functional group)

Gln : Glutamine

Glu : Acide glutamique

HCTU : *O*-(6-Chlorobenzotriazol-1-yl)-*N,N,N',N'*-tétraméthyluronium hexafluorophosphate

Hex : Hexanes

His : Histidine

HMPA : Hexaméthylphosphoramide

*i*Pr : *Iso*-propyle

IR : Infrarouge

L : Ligand

Lys : Lysine

m : Multiplet

MALDI-MS : Spectrométrie de Masse – Désorption-Ionisation Laser Assistée par Matrice (Matrix Assisted Laser Desorption Ionisation – Mass Spectrometry)

mCPBA : Acide métachloroperbenzoïque (metachloroperbenzoic acid)

Me : Méthyle

MeCN : Acétonitrile

MeOH : Méthanol

MOM : Méthoxyméthyl acétal

mmol : Millimole

NMP : *N*-Méthyl-2-pyrrolidone

nuit/o.n. : Nuit (overnight)

pf/mp : Point de fusion (melting point)

Ph : Phényle

Piv : Pivaloyle

PivO/OPiv : Pivaloate

Pyr : Pyridine

q : Quadruplet

quint : Quintuplet

R : Substituant (alkyle, aryle, H, etc.)

rac : Racémique

R_f : Rapport frontal

RMN/NMR : Résonance Magnétique Nucléaire (Nuclear Magnetic Resonance)

s : Singulet

Ser : Sérine

SMHR/HRMS : Spectrométrie de Masse à Haute Résolution (High Resolution Mass Spectrometry)

S_NAr : Substitution nucléophile aromatique

t : Triplet

TA/RT : Température ambiante (Room temperature)

*t*Bu : *Tert*-butyle

TCEP : *Tris*(2-carboxyéthyl)phosphine

td : Triplet de doublet

TFA : Acide trifluoroacétique ou trifluoroacétate

Tf : Triflyle

TfO/OTf :Triflate

TfOH : Acide trifluorométhanesulfonique

THF: Tétrahydrofurane

THP: Tétrahydropyrane

Thr : Thréonine

TM/MS : Tamis moléculaire (Molecular sieves)

TMG : *N,N,N',N'*-tétraméthylguanidine

Trp : Tryptophane

Trt : Trityle (Triphenylméthyle)

Ts : Tosyle

TsO/OTs : Tosylate

TsOH : Acide paratoluènesulfonique

Tyr : Tyrosine

Val : Valine

X : Hétéroatome (O, N, S, Cl, Br, I)

LISTE DES SYMBOLES ET DES UNITÉS

° : Degré

°C : Degrés Celsius

α : Alpha

Å : Ångström (10^{-10} mètres)

β : Béta

c : Centi (10^{-2})

cm^{-1} : Nombre d'onde (par centimètre)

δ : Delta (Déplacement chimique)

g : Gramme

h : Heure

Hz : Hertz

j/d : Jours (Days)

L : Litre

μ : Micro (10^{-6})

M : Méga (10^{6})

M : Mole par litre

m : Milli (10^{-3})

mins : Minutes

Mm : Masse molaire (g/mol)

ppm : Parties par million

^{TM} : Trademark

RÉSUMÉ

Dans les dernières décennies, les triarylbismuthines sont des espèces organométalliques qui ont gagné beaucoup d'intérêt en synthèse organique. Ces réactifs sont utilisés dans des réactions de couplages-croisés catalysés au palladium, pour former des liens C–C à partir d'halogénoaryles, et au cuivre pour former des liens C–N, C–O et C–S à partir de nucléophiles de type N–H, O–H et S–H.

Dans la littérature, Barton et Finet ont été en mesure d'aryler toutes sortes de substrats en utilisant des triarylbismuthines par catalyse au cuivre. Cependant, les travaux effectués sur le développement de méthodes d'arylation des chaînes latérales des acides aminés demeurent limités.

Au cours des dernières années, notre groupe de recherche a été en mesure de synthétiser une librairie d'organobismuthines hautement fonctionnalisés par la manipulation de groupes fonctionnels. D'autre part, nous avons été capable d'aryler une grande variété de substrats de type N–H et O–H tels que des indoles, des imidazoles, des phénols, des aminoalcools, etc. Sachant que ces groupes fonctionnels sont présents dans la structure des acides aminés, nous avons transposé nos méthodes à l'arylation d'acides aminés utilisant des triarylbismuthines hautement fonctionnalisés.

La modification des chaînes latérales d'acides aminés peut s'avérer très utile en chimie médicinale ou en biochimie. En effet, plusieurs médicaments possèdent des motifs d'acides aminés dans leur structure. En biochimie, il peut être utile de marquer certains acides aminés dans des peptides ou des protéines pour être en mesure de les suivre avec des techniques analytiques à travers des processus biochimiques.

Nous rapportons dans cet ouvrage le développement d'une méthode d'arylation de chaînes latérales d'acides aminés en utilisant des triarylbismuthines par catalyse au cuivre. En ajout, il s'avère que notre méthode d'arylation démontre une sélectivité

envers l'arylation de la tyrosine, que ce soit dans un contexte d'un acide aminé simple ou d'un oligopeptide. Conséquemment, nous nous sommes concentrés sur l'arylation de ce résidu en transférant des aryles hautement fonctionnalisés et nous avons mené des études de chimiosélectivité en effectuant l'arylation de la tyrosine sur un peptide contenant un autre résidu possiblement réactif, notamment le tryptophane.

Mots clés :

- Triarylbismuthines
- Couplage-croisé
- Catalyse au cuivre
- Arylation d'acides aminés et de peptides

CHAPITRE I
BISMUTH

1.1. Historique du bismuth

Le bismuth est un métal lourd qui fait partie du 15^{e} groupe du tableau périodique, soit le groupe de l'azote, autrement appelé les pnictogènes (N, P, As, Sb, Bi). Le bismuth métallique (Bi^{0}) possède la configuration électronique [Xe] $4f^{14}$ $5d^{10}$ $6s^{2}$ $6p^{3}$ et il possède également deux formes d'oxydation stables, notamment le bismuth trivalent (Bi^{+3}), où il y a la perte de ses 3 électrons dans les orbitales $6p^{3}$ ([Xe] $4f^{14}$ $5d^{10}$ $6s^{2}$ $6p^{0}$), ainsi que le bismuth pentavalent (Bi^{+5}), où il y a la perte subséquente de ses 2 électrons dans l'orbitale $6s^{2}$ ([Xe] $4f^{14}$ $5d^{10}$ $6s^{0}$ $6p^{0}$).[1]

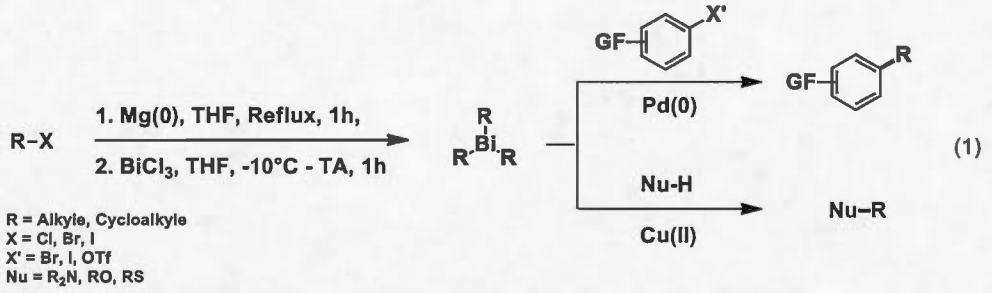
Ce métal a été découvert en 1753 par Claude Geoffroy le Jeune en le séparant du plomb.[2] La synthèse du triéthylbismuthine, soit un trialkylbismuthine, était le premier complexe organométallique de bismuth rapporté en 1850 par Löwig et Schweizer.[3] Par la suite, la première synthèse de triarylbismuthine a été effectuée en 1887 par Michaëlis et Polis.[4] Finalement, la synthèse des premiers tétraarylbismuthines et pentaarylbismuthines a été publiée en 1952 par Wittig et Clauss.[5]

Comme il a été mentionné antérieurement, les organobismuthines se divisent principalement en trois catégories, notamment les trialkylbismuthines, les triarylbismuthines et les triarylbismuthines pentavalents.

1.2. Trialkylbismuthines

Malgré leur utilité en synthèse organique, les trialkylbismuthines comportent certains désavantages. Par exemple, ceux-ci sont très instables, car ils sont pyrophoriques, ce qui nécessite qu'ils soient manipulés sous atmosphère inerte.[1] Compte tenu de ceci, ces derniers doivent être préparés *in situ* en ajoutant un bromure d'alkylmagnésium sur du $BiCl_3$. Par la suite, le trialkylbismuthine peut être impliqué

dans une réaction de couplage-croisé catalysée au Pd(0), en rajoutant un halogénoaryle, ou au Cu(II), en rajoutant un nucléophile de type N–H, O–H ou S–H (voir **Éq 1**).[6,7]

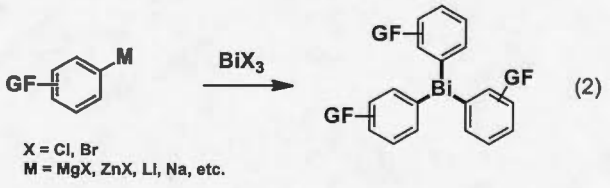


Éq 1 : Synthèse de trialkylbismuthines et emploi dans des réactions de couplages-croisés catalysés au Pd(0) ou au Cu(II)

1.3. Triarylbismuthines

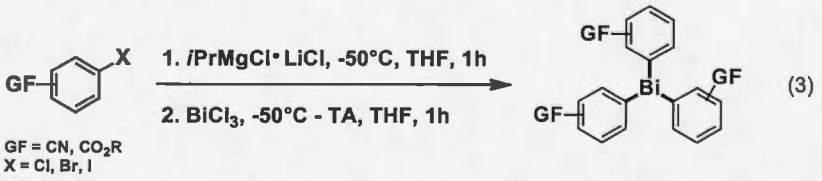
Les triarylbismuthines sont beaucoup plus stables que les trialkylbismuthines. En effet, ces derniers sont stables à l'eau et à l'air. De plus, ils peuvent être entreposés pendant plusieurs mois jusqu'à plusieurs années à température ambiante. En ajout, il est possible de les purifier par chromatographie sur colonne de silice ou par cristallisation. D'ailleurs, il a été rapporté que les sels de bismuth possèdent une faible toxicité en comparaison à d'autres métaux de transition utilisés pour effectuer des couplages-croisés tel que l'étain. En effet, on retrouve le bismuth dans certains médicaments qui sont vendus sur le marché, tels que le subsalicylate de bismuth (Peptobismol) ainsi que le subcitrate de bismuth (CBS; De-Nol).[8] En outre, il s'avère que les triarylbismuthines tolèrent une grande variété de groupes fonctionnels ce qui les rend très utiles en développement de méthodes.[9] En ajout, les réactifs d'organobismuth sont considérés comme étant très versatiles ce qui explique leur application en synthèse totale,[10] pour la préparation de complexes organométalliques comportant des métaux de transition,[11] en tant que catalyseurs pour des réactions de polymérisation,[12] ainsi qu'en chimie médicinale.[13]

En ce qui concerne la synthèse des triarylbismuthines, $BiAr_3$, ces derniers sont facilement accessibles en formant une espèce organométallique, tel qu'un réactif de Grignard, à partir d'un halogénoaryle et du magnésium métallique, et en l'ajoutant sur un sel de bismuth, souvent le $BiCl_3$.[14] Il est à noter que les triarylbismuthines peuvent également être synthétisés à partir d'autres sources organométalliques telles que des organozinciques,[15] des organolithiens,[16] (voir **Éq 2**) etc. Dans le cas où il y aurait des groupes fonctionnels (GF) sensibles au caractère nucléophile des réactifs de Grignard, tels qu'un ester ou un nitrile, il est préférable d'employer les conditions de Knochel afin de préparer ces organobismuthines respectifs (voir **Éq 3**).[17]



(2)

Éq 2 : Synthèse de triarylbismuthines par ajout de réactifs organomagnésiens, organozinciques, organolithiens ou organosodiques sur un sel de bismuth



(3)

Éq 3 : Synthèse de triarylbismuthines portant des groupes fonctionnels sensibles en employant les conditions de Knochel

Dans notre laboratoire, nous avons été capables de préparer une variété d'organobismuthines en employant cette méthode (voir **Schéma 1**). En utilisant cette méthode de synthèse directe, nous avons accès à plusieurs groupes fonctionnels tels que des des alkyles, des cycloalkyles, des fluorures, des trifluorométhyles, des méthoxys, des acétals d'aldéhyde, des acétals de phénol, ainsi que des noyaux

hétéroaromatiques. D'ailleurs, il est possible d'obtenir des aryles substitués dans les positions *ortho*, *méta*, *para*, ainsi que des aryles polysubstitués. Il est à noter que les rendements des triarylbismuthines substitués en *ortho,* ainsi que les dérivés polysubstitués, sont plus faibles, tout probablement en raison de l'encombrement stérique présent sur ces molécules. D'autre part, lors de la purification par chromatographie des acétals d'aldéhydes, il est possible d'observer l'hydrolyse de la fonction acétal en aldéhyde en raison du caractère acide de la silice. Pour contourner ce problème, il peut être prudent de conditionner la colonne préalablement avec de la triéthylamine, Et_3N, dans l'éluant afin de réduire l'acidité de la silice. Ensuite, pour s'assurer que la colonne demeure relativement basique, il est mieux de continuer à ajouter un peu de triéthylamine dans l'éluant pendant la purification. En opposition, le phénol protégé par le groupement THP (tétrahydropyranne) est assez robuste pour résister à l'acidité de la silice, donc l'emploi de triéthylamine n'est pas nécessaire pour sa purification.

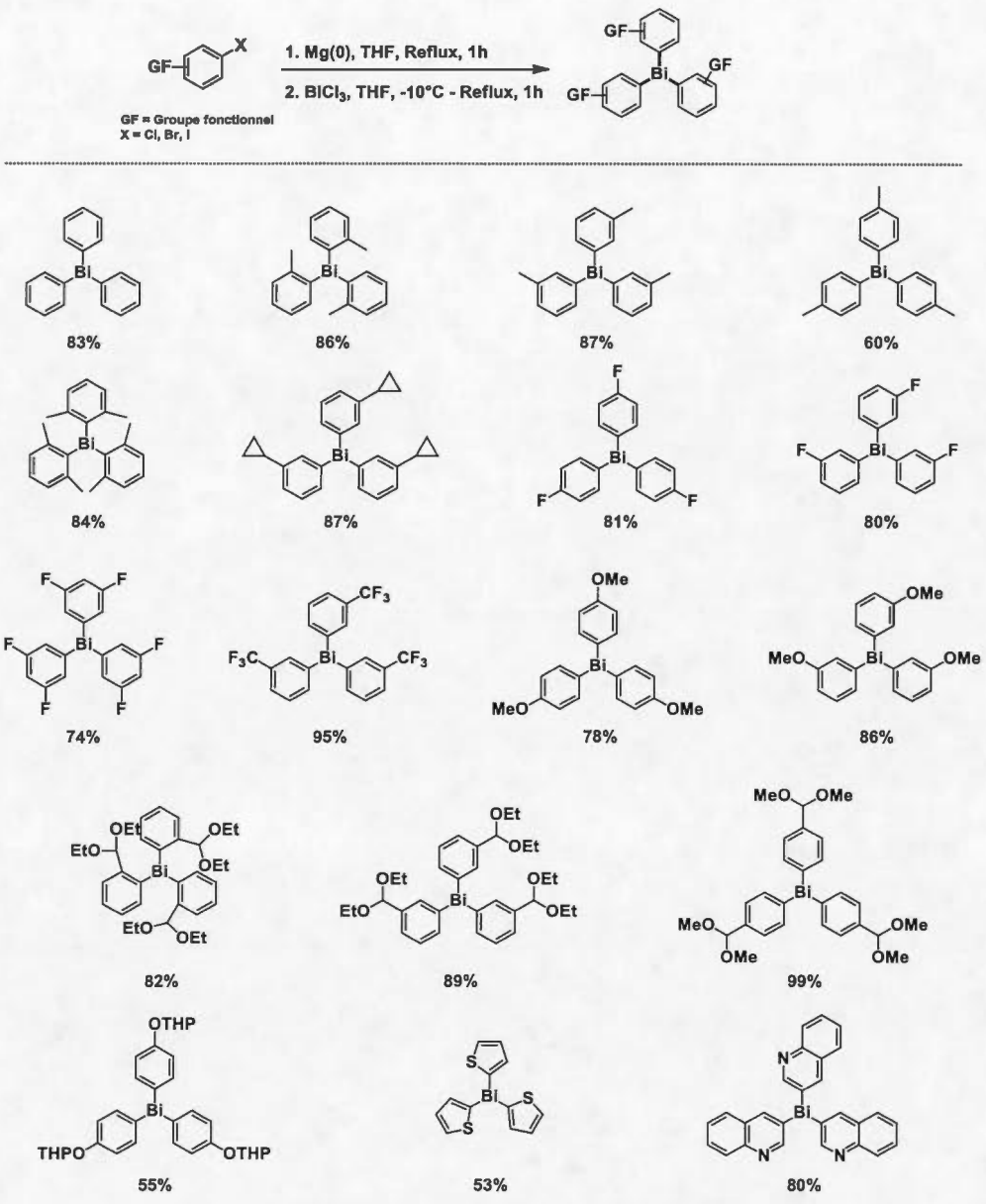


Schéma 1 : Préparation d'organobismuthines fonctionnalisés

1.4. Synthèse d'organobismuthines hautement fonctionnalisés et dérivatisation

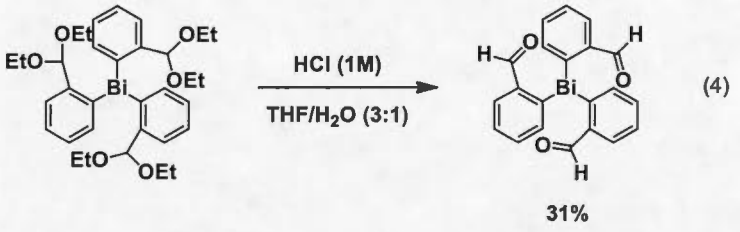
Comme il a été mentionné antérieurement, certains groupements fonctionnels contenant des entités électrophiles tels que des carbonyles (aldéhyde, cétone, ester) ou des nitriles ne peuvent pas être synthétisés directement en utilisant cette méthode en

raison de leur sensibilité à la forte nucléophilie des réactifs de Grignard formés lors de cette transformation.

Or, il est possible de préparer des réactifs de Grignard contenant des groupes fonctionnels sensibles, tels que des esters et des nitriles, en employant les conditions de Knochel (voir **Éq 3**). D'abord, il est important de savoir que la réaction d'échange halogène-métal Br/Li est beaucoup plus rapide que l'échange Br/Mg.[18] De plus, l'échange Br/Li est effectué à basse température, alors que l'échange Br/Mg exige un chauffage, ce qui n'est pas compatible avec plusieurs groupes fonctionnels. Aussi, la réaction d'échange Br/Mg est particulièrement lente pour les halogénoaryles riches en électrons, ce qui fait en sorte que la réaction d'échange entre en compétition avec l'élimination de HBr du 2-bromopropane (formé lors de l'échange avec *i*PrMgCl). Pour contourner ces problèmes, on effectue la réaction d'échange à basse température (entre -50°C et -20°C) avec une solution contenant du *i*PrMgCl•LiCl, soit dans les conditions de Knochel. L'ajout du sel de lithium, soit le chlorure de lithium (LiCl), fait en sorte que la réaction d'échange halogène-métal est de type Br/Li et permet que celle-ci soit rapide. De plus, elle est effectuée à basse température ce qui permet que les fonctions sensibles (ester, nitrile) ne soient pas touchées. D'ajout, puisque la réaction d'échange Br/Li est beaucoup plus rapide que l'échange Br/Mg, on évite la compétition avec l'élimination de HBr du 2-bromopropane.[17] Également, des triarylbismuthines ayant des groupes fonctionnels comprenant de protons acides (OH, NH, SH) ne pourront pas être préparés par cette méthode dû au caractère basique des réactifs de Grignard formés pendant la réaction.

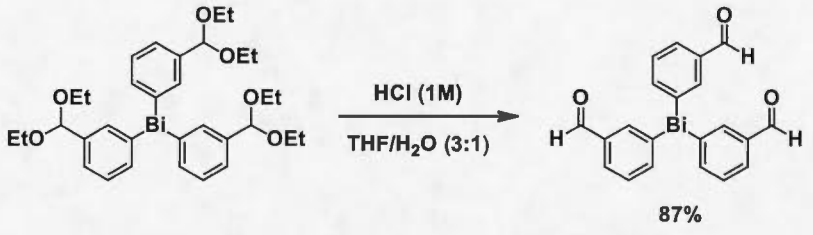
Comme il a été illustré au **Schéma 1**, la méthode de préparation directe d'organobismuthines donne accès à quelques fonctionnalités, mais celles-ci demeurent relativement simples et limitées. Cependant, il est possible d'effectuer une dérivatisation de groupe fonctionnel directement sur l'organobismuthine afin d'obtenir une fonction plus élaborée. Par exemple, en mettant les dérivés 2- ou 3-

diéthoxyméthyles en condition acide aqueuse, la fonction acétal s'hydrolyse cédant ainsi les dérivés 2- et 3-formyles (voir **Éqs 4** et **5**).



(4)

Éq 4 : Hydrolyse de la fonction acétal du dérivé 2-diéthoxyméthyle en 2-formyle



(5)

Éq 5 : Hydrolyse de la fonction acétal du dérivé 3-diéthoxyméthyle en 3-formyle

Avec les dérivés formyles en main, on peut prendre avantage de la versatilité de la fonction aldéhyde pour donner un accès à une variété de groupes fonctionnels intéressants. Premièrement, en ajoutant du bromure de méthylmagnésium sur le dérivé 3-formyle, le dérivé possédant un alcool secondaire est obtenu. Subséquemment, cet alcool peut être oxydé en cétone soit par le periodinane de Dess-Martin ou par oxydation de Swern. Deuxièmement, la réduction de l'aldéhyde en alcool primaire est effectuée grâce au borohydrure de sodium ($NaBH_4$). Finalement, une réaction de Wittig peut être effectuée sur la fonction aldéhyde afin d'obtenir les dérivés ester α,β-insaturé et vinyle (voir **Schéma 2**). D'autre part, l'addition de bromure de méthylmagnésium sur l'ester méthylique mène au dérivé comprenant un alcool tertiaire (voir **Éq 6**). En résumé, les organobismuthines sont des composés robustes qui sont capables de résister aux conditions acides, basiques, et ils peuvent tolérer la présence de nucléophiles, d'oxydants et de réducteurs (voir **Éqs 4-6** et **Schéma 2**).

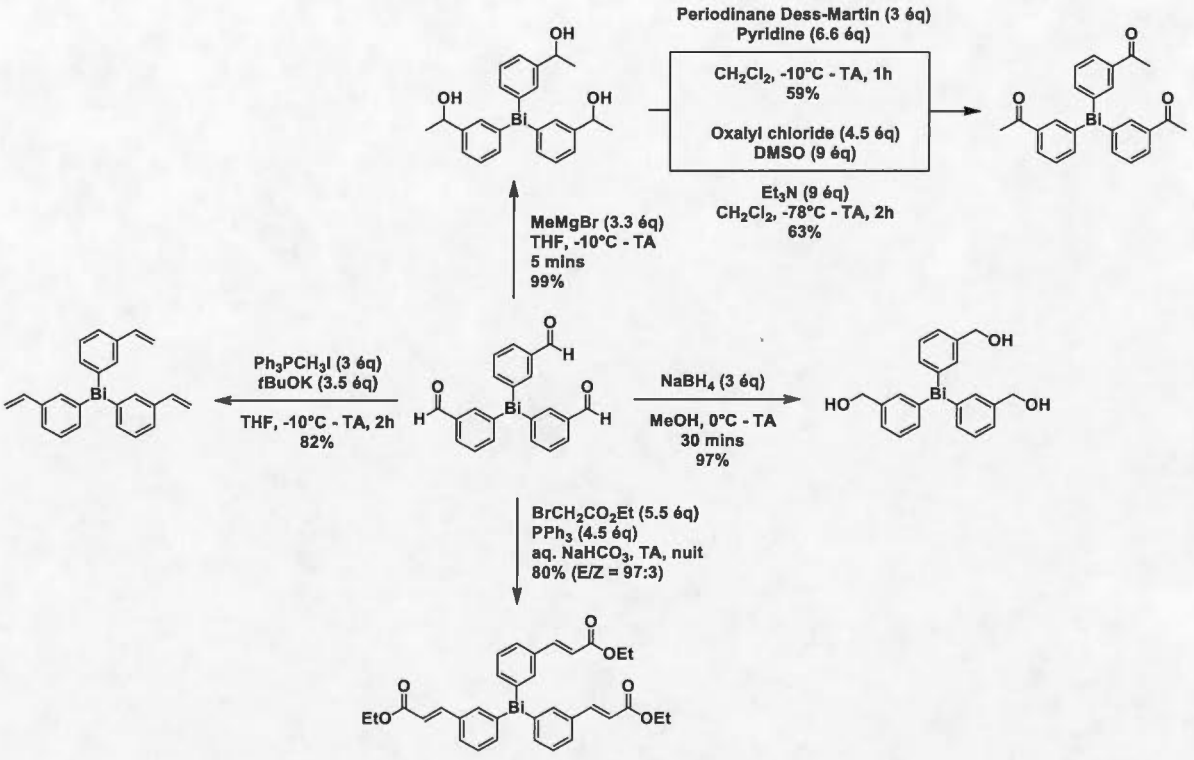
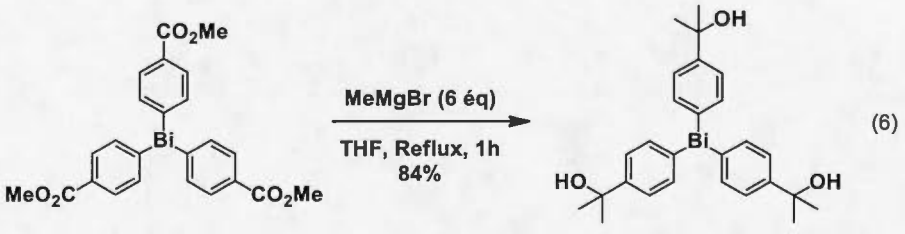


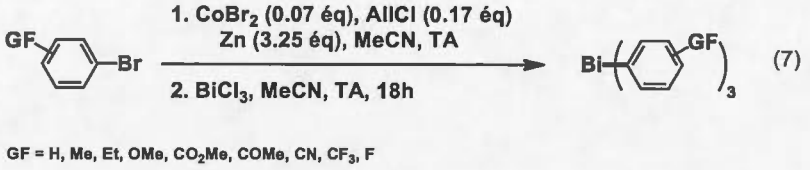
Schéma 2 : Dérivatisation de la fonction aldéhyde du dérivé 3-formyle



Éq 6 : Dérivatisation de la fonction ester en alcool tertiaire

Condon a rapporté une méthode très puissante pour synthétiser des organobismuthines hautement fonctionnalisés en passant par un échange halogène-métal catalysé au cobalt et au zinc. Cette méthode permet de former des triarylbismuthines hautement fonctionnalisés directement à partir d'halogénures d'aryles fonctionnalisés (contenant des fonctions telles que des esters, des nitriles, des

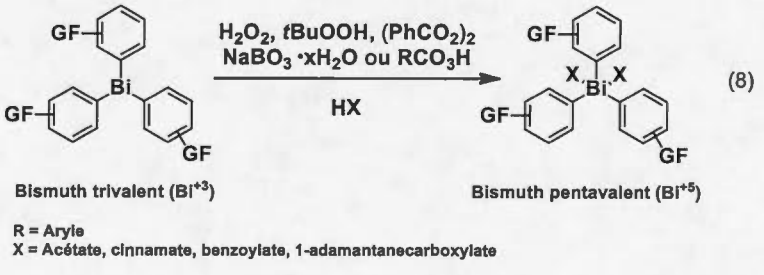
cétones, etc.), une quantité catalytique de bromure de cobalt(II), un excès de poudre de zinc et du chlorure d'allyle (voir **Éq 7**).[15]



Éq 7 : Synthèse de triarylbismuthines hautement fonctionnalisés via un échange halogène-métal catalysé au cobalt et au zinc

1.5. Triarylbismuthines pentavalents

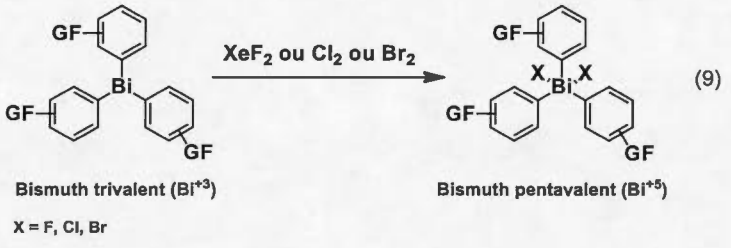
Les triarylbismuthines pentavalents peuvent être obtenus en effectuant une oxydation sur le triarylbismuthine correspondant. Pour ce faire, on doit ajouter un oxydant au triarylbismuthine, ainsi qu'un acide tel que l'AcOH. Dans la littérature, on retrouve souvent que cette réaction emploie des peroxydes, tels que le H_2O_2, le *t*BuOOH, le $(PhCO_2)_2$ et le $NaBO_3 \cdot xH_2O$ ou des peracides, RCO_3H, en présence d'un acide HX (où R = Aryle, X = acétate, cinnamate, benzoylates substitués et 1-adamantanecarboxylate) (voir **Éq 8**).[19]



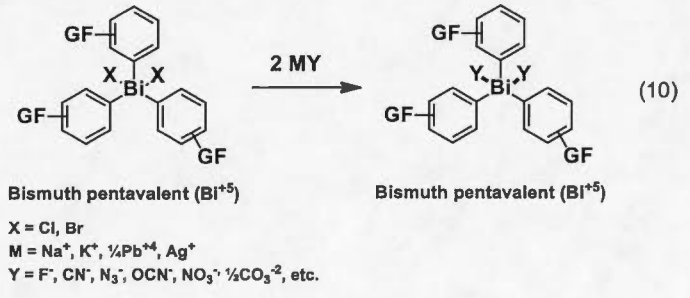
Éq 8 : Oxydation de triarylbismuthines en ses homologues pentavalents par ajout de peroxyde, de peracide ou de perborate de sodium

Par ailleurs, il est possible de synthétiser les difluoro-, dichloro- et dibromotriarylbismuthines en oxydant le triarylbismuthine correspondant avec soit du

XeF_2, du Cl_2 ou du Br_2 (voir **Éq 9**).[4,20] Or, l'ajout d'I_2 sur un $BiAr_3$ ne donnera pas son analogue diiodo- pentavalent, mais plutôt du Ar_2BiI et du ArI.[20] Une fois que les dérivés pentavalents dichloro- et dibromo- sont obtenus, il est possible de substituer le chlore ou le brome par d'autres anions tels que F^-, CN^-, N_3^-, OCN^-, NO_3^-, CO_3^{-2} AcO^- et TfO^- en ajoutant des sels de sodium, potassium, plomb ou argent (voir **Éq 10**).[21,22] Les sels d'argent, tels que AgOTf, fonctionnent particulièrement bien car l'argent piège les halogènes en formant des précipités très peu solubles, soient AgCl et AgBr, ce qui permet la substitution du chlore et du brome par des anions moins nucléophiles tels que TfO^-.



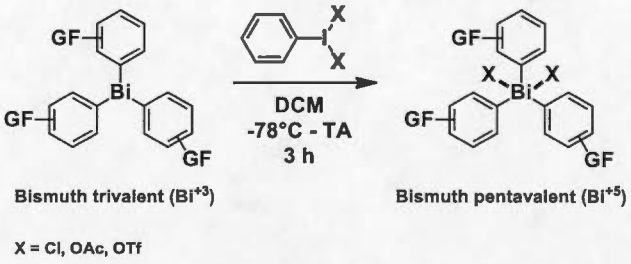
Éq 9 : Oxydation de triarylbismuthines en ses homologues pentavalents par ajout de XeF_2, de Cl_2 ou de Br_2



Éq 10 : Substitution d'ions de chlore ou de brome par d'autres anions

Par ailleurs, il est aussi possible de transformer le bismuth trivalent en bismuth pentavalent à l'aide d'iode hypervalent. Par exemple, on peut synthétiser du $BiAr_3X_2$ en rajoutant du $PhIX_2$, où X = Cl, OAc ou OTf, au $BiAr_3$ correspondant (voir **Éq 11**).

Cette réaction permet d'obtenir le produit désiré, ainsi que de l'iodobenzène qui peut être enlevé *in vacuo*.[22]



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Éq 11 : Oxydation de triarylbismuthines en ses homologues pentavalents par ajout d'iode hypervalent

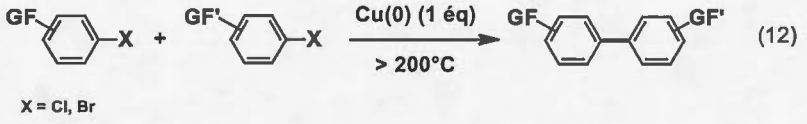
Les réactifs de bismuth pentavalent peuvent être difficiles, voire impossible à purifier sur silice, donc ils sont soit préparés *in situ* et ensuite utilisés pour effectuer des réactions de couplages-croisés, ou ils sont purifiés par recristallisation.

De plus, il est possible de réduire les organobismuthines pentavalents en leur analogues trivalents en utilisant des agents réducteurs tels que l'hydrazine hydrate ($NH_2NH_2 \cdot xH_2O$), le dithionite de sodium ($Na_2S_2O_4$), l'ammoniac liquide ($NH_{3(l)}$), l'hydrure d'aluminium et de lithium ($LiAlH_4$), le borohydrure de sodium ($NaBH_4$) et le sulfure de sodium (Na_2S).[20]

CHAPITRE II
COUPLAGES-CROISÉS CATALYSÉS AU CUIVRE

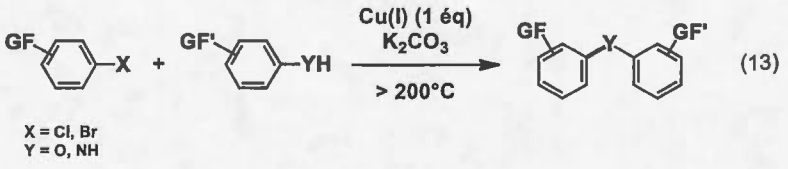
2.1. Couplages-croisés catalysés au Cu(0)

C'est en 1901 que Fritz Ullmann a découvert que la synthèse de biaryles pouvait être effectuée en faisant réagir des halogénoaryles avec une quantité stœchiométrique de cuivre métallique en chauffant à plus de 200°C (voir **Éq 12**).[23] Par la suite, en 1903, Ullmann a rapporté les premiers exemples d'arylation de nucléophiles, soient des anilines et des phénols, encore une fois en employant une quantité stœchiométrique de Cu(I) en chauffant à plus de 200°C, mais cette fois-ci en ajoutant une base (K_2CO_3) (voir **Éq 13**).[24] En 1906, Irma Goldberg a démontré qu'il était possible d'effectuer cette dernière transformation en utilisant une quantité substœchiométrique de cuivre.[25]



(12)

Éq 12 : Synthèse de biaryles par couplage d'Ullmann catalysé au Cu(0)



(13)

Éq 13 : Synthèse de biaryléthers et de biarylamines par couplage d'Ullmann catalysé au Cu(I)

La découverte du couplage d'Ullmann-Goldberg fût très importante pour la formation de liaisons C–N, C–O et C–S en chimie du cuivre. Toutefois, cette réaction nécessite des conditions relativement extrêmes, dont des températures de réaction au-dessus de 200°C. Conséquemment, plusieurs groupes de recherche se sont mis à travailler sur des moyens pour effectuer ces réactions de couplage en utilisant des conditions plus douces. À cet effet, la grande majorité des couplages de type N–H, O–

H et S–H catalysés au cuivre rapportés dans la littérature utilisent plutôt des catalyseurs de Cu(I) ou de Cu(II) avec ou sans l'ajout de ligands.

2.2. Ligands employés lors des couplages-croisés catalysés au cuivre

Le cuivre, se retrouvant à l'extrême droite de la première période des métaux de transition, est considéré comme un métal relativement dur, ce qui signifie que son rayon atomique est relativement petit et que sa charge est plus concentrée autour de son noyau (contrairement au palladium). Cela étant dit, il va préférer se lier à des ligands durs contenant des atomes d'oxygène et d'azote. Par exemples, des ligands de type *N,N*- (tels que des α-diimines, des 1,2-diamines, des phénanthrolines, etc.), de type *O,O*- (tels que des 1,3-dicétones, des 1,2-diols, des 1,3-triols, etc.) et de type *N,O*- (tels que des dérivés d'acides aminés (glycine, proline), des 1,2-aminoalcools, des hydroxyquinolines etc.) sont capables d'activer les catalyseurs de cuivre en se liant à ce dernier (voir **Schéma 3**). La formation de ces complexes de cuivre *in situ* engendre souvent une augmentation du rendement de la réaction de couplage et cette variation peut aussi permettre d'effectuer la réaction dans des conditions plus douces.[26]

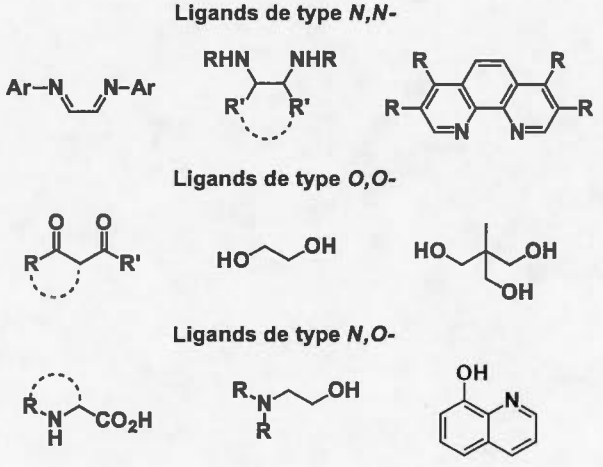
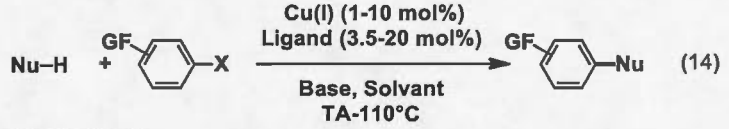


Schéma 3 : Exemples de ligands de type *N,N*-, *O,O*- et *N,O*- employés dans des couplages-croisés catalysés au cuivre

2.3. Couplages-croisés catalysés au Cu(I)

Typiquement, les couplages-croisés catalysés au cuivre utilisent soit une source de Cu(I) ou de Cu(II). En ce qui concerne la catalyse au Cu(I), les catalyseurs les plus fréquemment utilisés sont : CuCl, CuBr, CuI, CuCN, Cu_2O et $CuBr{\bullet}SMe_2$. Les conditions typiques d'une réaction de couplage d'un nucléophile de type N–H, O–H ou S–H sont : une quantité catalytique de Cu(I) (1-10 mol%), un ligand (3.5-20 mol%), une base (K_2CO_3, K_3PO_4, Cs_2CO_3, KOH) et un halogénoaryle (Br, I). Ces réactions peuvent être effectuées à température ambiante, mais elles nécessitent souvent un chauffage (40-110°C) (voir **Éq 14**).



Nu = NR_2, OR, SR
X = Br, I
Cu(I) = CuCl, CuBr, CuI, CuCN, Cu_2O, $CuBr{\bullet}SMe_2$
Base = K_2CO_3, K_3PO_4, Cs_2CO_3, KOH
Solvant = Toluène, Dioxane, NMP, DMF

Éq 14 : Arylation de nucléophiles de type N–H, O–H ou S–H par couplage de Buchwald utilisant des halogénures d'aryles catalysés au Cu(I) avec l'ajout de ligands

Cette réaction est possible en utilisant une quantité catalytique de cuivre, car le Cu(I) est régénéré à la fin du couplage-croisé. D'abord, il y a substitution de l'halogène du cuivre, Y, par le nucléophile, Nu (voir étape **A**). Par la suite, il y a addition oxydante du Cu(I) dans la liaison Ar–X, formant ainsi un espèce de Cu(III) (voir étape **B**). Finalement, il y a élimination réductrice qui mène à la formation de la liaison entre le nucléophile et l'aryle, régénérant ainsi le Cu(I) (voir étape **C**). Il est à noter que l'étape d'addition oxydante est réversible, donc on peut aussi reformer l'halogénure d'aryle (Ar–X) comme réaction secondaire. Dans ce mécanisme, il est aussi possible de voir la formation d'un complexe entre les ligands bidendates (de type *O,O*-, *N,O*- et *N,N*-) mentionnés dans la section précédente et le cuivre (voir **Schéma 4**).[27]

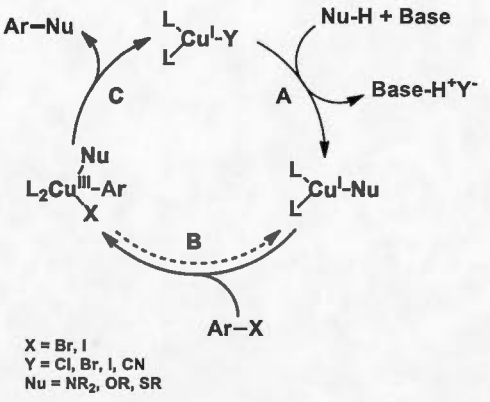
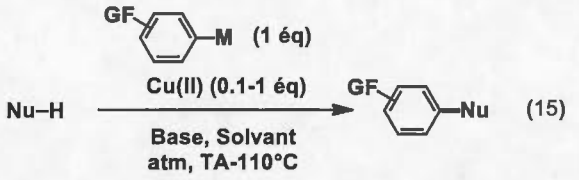


Schéma 4 : Cycle catalytique d'un couplage-croisé catalysé au Cu(I)

2.4. Couplages-croisés catalysés au Cu(II)

Également, des nucléophiles de types N–H, O–H et S–H peuvent être arylés par une réaction de couplage-croisé catalysé au Cu(II) en utilisant des acides boroniques, des aryltrifluoroborates de potassium ou des organobismuthines (trivalents et pentavalents) comme source d'aryle, soit une réaction de type Chan-Evans-Lam. Le catalyseur le plus fréquemment utilisé pour effectuer cette transformation est le $Cu(OAc)_2$, mais d'autres catalyseurs tels que $Cu(OAc)_2 \cdot H_2O$, $Cu(OTf)_2$, $Cu(OPiv)_2$, $Cu(TFA)_2$, $Cu(acac)_2$ et $Cu(NO_3)_2$ peuvent être utilisés. Cette réaction est souvent effectuée dans le DCM ou le toluène dans des gammes de températures entre la température de la pièce jusqu'à 110°C. Cette réaction requiert aussi l'ajout d'une base, typiquement la pyridine ou la Et_3N afin de capturer le proton du nucléophile lors de la substitution d'un ligand sur le cuivre (voir **Éq 15**).



Nu = NR_2, OR, SR
M = $B(OH)_2$, BF_3K, $BiAr_2$, $BiAr_2(OAc)_2$
Cu(II) = $Cu(OAc)_2$, $Cu(OAc)_2$ H_2O, $Cu(OTf)_2$, $Cu(OPiv)_2$, $Cu(TFA)_2$, $Cu(acac)_2$, $Cu(NO_3)_2$
Base = Pyridine, Et_3N
Solvent = DCM, Toluène
atm = Air, O_2

Éq 15 : Arylation de nucléophiles de type N–H, O–H ou S–H par couplage de type Chan-Evans-Lam utilisant des acides boroniques, des trifluoroborates de potassium ou des triarylbismuthines (trivalents et pentavalents)

Les réactions de couplage-croisé catalysées au Cu(II) passent par un mécanisme différent de celles catalysées au Cu(I). En effet, les réactions catalysées au Cu(I) utilisent des halogénoaryles comme source d'aryle et peuvent utiliser une quantité catalytique de cuivre, car il est régénéré à la fin de la réaction de couplage-croisé.

Or, dans le cas des réactions de couplage-croisé catalysées au Cu(II), celles-ci peuvent employer une quantité substœchiométrique de cuivre si elles sont effectuées sous air ou O_2. Notamment, le mécanisme de réaction implique l'emploi d'une source de Cu(II), souvent $Cu(OAc)_2$, où il y a substitution d'un acétate, X, par le nucléophile, Nu (voir étape **A**). Ensuite, il y a transmétallation d'un aryle sur le cuivre (voir étape **B**). Par la suite, l'espèce formée peut passer par deux différents parcours, soit le parcours **C-D**, soit le parcours **E-G**. D'une part, dans le parcours **C-D**, il y a élimination réductrice accompagnée de la formation du produit désiré, Ar–Nu, et du Cu(0) (voir étape **C**). Ensuite, le Cu(0) est oxydé en Cu(II), fermant ainsi le cycle catalytique (voir étape **D**). D'autre part, dans le parcours **E-G**, l'espèce de Cu(II) est oxydée en Cu(III) à l'aide d'O_2 (voir étape **E**). Après cela, le produit désiré est formé par élimination réductrice, livrant ainsi un espèce de Cu(I) (voir étape **F**) qui peut subséquemment se faire oxyder en Cu(II) en présence d'O_2 (voir étape **G**). Il est à noter qu'il n'y a toujours pas un accord définitif du mécanisme du couplage-croisé de type Chan-Evans-Lam

catalysé au Cu(II) parmi la communauté scientifique. Cependant, selon Lam,[28] l'étape d'élimination réductrice **C** serait très lente, alors que celle de l'étape **F** serait rapide, suggérant que le parcours **E-G** serait plus probable que le parcours **C-D** (voir **Schéma 5**).

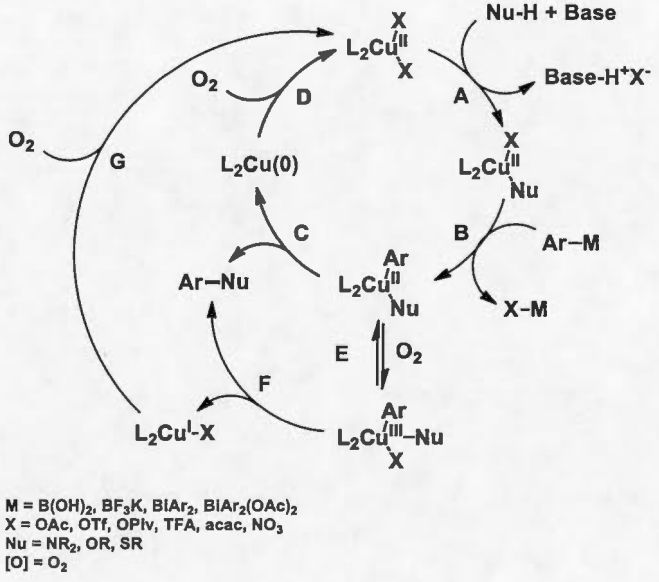
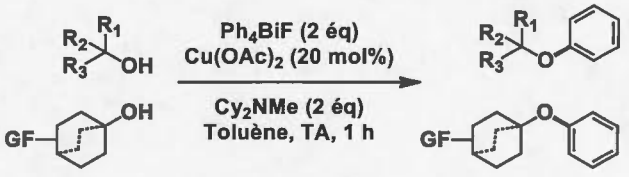


Schéma 5 : Cycle catalytique d'un couplage-croisé catalysé au Cu(II) de type Chan-Evans-Lam

Parallèlement, certains groupes de recherche ont rapporté l'arylation de nucléophiles catalysée au Cu(II) en utilisant des triarylbismuthines pentavalents préparés en avance ou *in situ*. En ce qui concerne la préparation *in situ* des triarylbismuthines pentavalents, on doit ajouter un oxydant, tel que de l'OXONE™ (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), un peracide ($CH_3CO_3H$) ou de l'iode hypervalent ($PhI(OAc)_2$), sur le triarylbismuthine trivalent correspondant pour oxyder le Bi(III) en Bi(V).[29] Cependant, cette approche n'est pas convenable pour des triarylbismuthines portant des fonctionnalités sensibles aux conditions oxydantes.

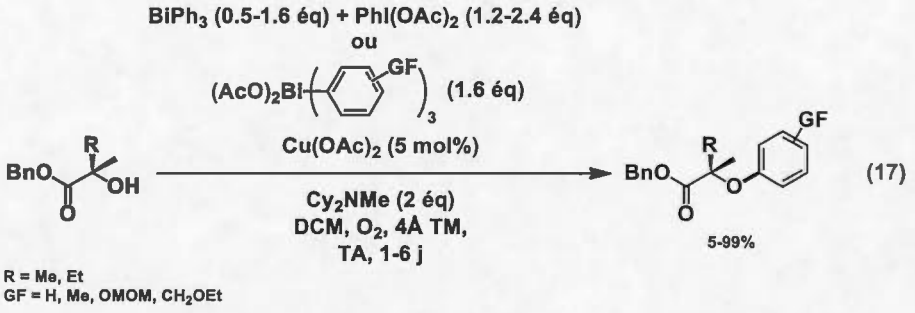
2.4.1. Formation de liens C–O via des couplages-croisés catalysés au Cu(II) utilisant des organobismuthines

Certains groupes de recherche ont développé des méthodes de *O*-arylation d'alcools aliphatiques en utilisant des réactifs d'organobismuth. Par exemple, le groupe de Mukaiyama[30] a été en mesure d'aryler des alcools 1°, 2° et 3° facilement en utilisant des tétraarylbismuthines par catalyse au Cu(II) (voir **Éq 16**).

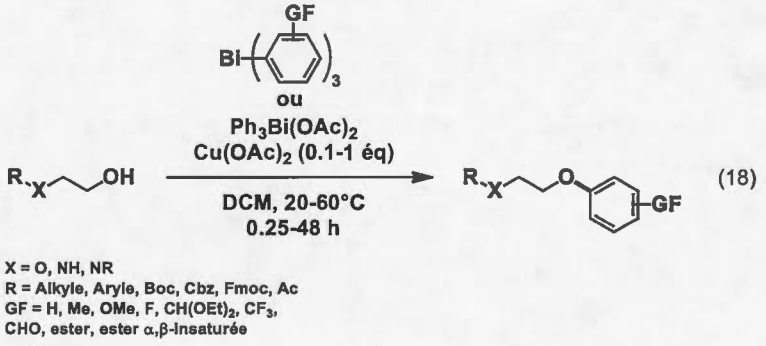


Éq 16 : Arylation d'alcools aliphatiques par couplage-croisé catalysé au Cu(II) en utilisant des organobismuthines pentavalents

De plus, d'autres groupes ont réussi à aryler des alcools ayant des groupes électroattracteurs à proximité de la fonction hydroxyle. Notamment, le groupe de Sato[31] a rapporté une méthode d'arylation d'α-hydroxy esters en utilisant des organobismuthines pentavalents préparés en avance, ou formés *in situ* en rajoutant du $PhI(OAc)_2$ comme oxydant sur du $BiPh_3$ (oxydation du Bi(III) en Bi(V)) et une quantité catalytique du catalyseur de Cu(II) (voir **Éq 17**). D'ailleurs, les groupes de Gagnon[32a] et Barton[32b] ont été en mesure d'aryler des 1,2-aminoalcools et des 1,2-alcoxyalcools en utilisant des triarylbismuthines (trivalents ou pentavalents) et une quantité substœchiométrique du catalyseur de Cu(II) (voir **Éq 18**). Selon les travaux du groupe de Gagnon, il semblerait y avoir un lien entre la tendance de l'alcool à se faire aryler et de la présence d'un groupe électroattracteur à proximité de ce dernier.[32a]

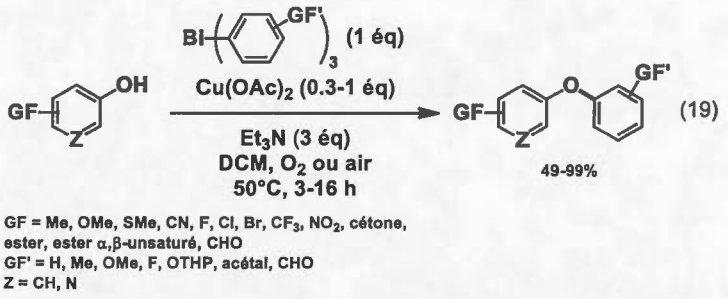


Éq 17 : Arylation d'α-hydroxy esters par couplage-croisé catalysé au Cu(II) en utilisant des triarylbismuthines pentavalents



Éq 18 : Arylation d'alcools comportant des groupes électroattracteurs par couplage-croisé catalysé au Cu(II) en utilisant des triarylbismuthines trivalents et pentavalents

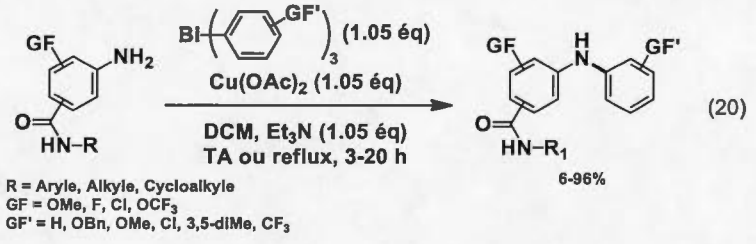
D'ajout, le groupe de Gagnon[33] a développé une méthode permettant la préparation de biaryléthers par arylation de phénols en utilisant des triarylbismuthines fonctionnalisés par catalyse au Cu(II) (voir **Éq 19**).



Éq 19 : Arylation de phénols par couplage-croisé catalysé au Cu(II) en utilisant des triarylbismuthines

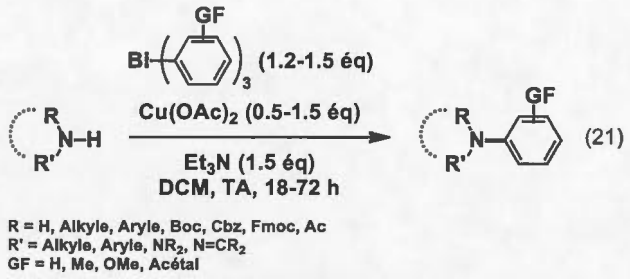
2.4.2. Formation de liens C–N via des couplages-croisés catalysés au Cu(II) utilisant des organobismuthines

En ce qui concerne la *N*-arylation de substrats par catalyse au cuivre, Sorenson[34] a été en mesure d'aryler des anilines substitués avec des triarylbismuthines et une quantité suprastœchiométrique d'acétate de Cu(II) (voir **Éq 20**).



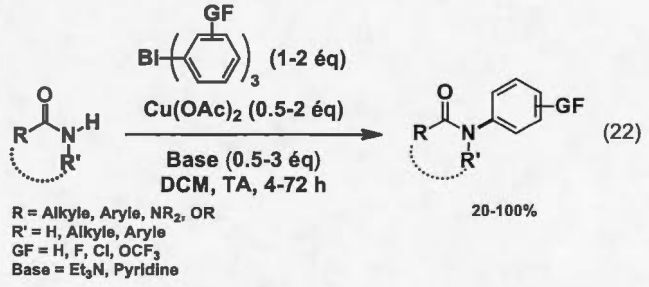
Éq 20 : Arylation d'anilines par couplage-croisé catalysé au Cu(II) en utilisant des triarylbismuthines

D'autres substrats tels que des amines[35], des hydrazines[36] et des hydrazones[37] ont pu être *N*-arylés en employant des triarylbismuthines et de l'acétate cuprique (voir **Éq 21**).



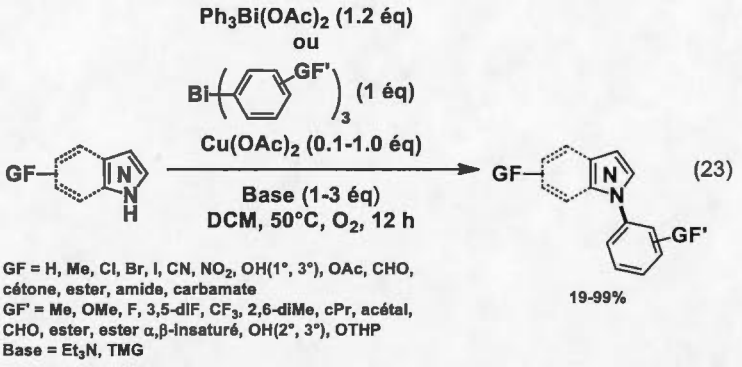
Éq 21 : Arylation d'amines, d'hydrazines et d'hydrazones par couplage-croisé catalysée au Cu(II) en utilisant des triarylbismuthines

De même, il est possible d'effectuer l'arylation d'amides, de carbamates et d'urées en utilisant des triarylbismuthines par catalyse à l'acétate de cuivre (voir **Éq 22**).[38]



Éq 22 : Arylation d'amides par couplage-croisé catalysée au Cu(II) en utilisant des triarylbismuthines

Finalement, une variété d'hétérocycles azotés (incluant les indoles, les benzimidazoles, les indazoles, les pyrroles, les pyrazoles, les imidazoles, etc.) peuvent être *N*-arylés en employant des triarylbismuthines trivalents ou pentavalents par catalyse au Cu(II) (voir **Éq 23**).[39]



Éq 23 : Arylation d'hétérocycles azotés par couplage-croisé catalysée au Cu(II) en utilisant des triarylbismuthines trivalents et pentavalents

CHAPITRE III
COUPLAGES-CROISÉS CATALYSÉS AU PALLADIUM

3.1. Sources organométalliques

La catalyse au palladium a révolutionné la manière que l'on crée de nouveaux liens C–C. En effet, en combinant un halogénoaryle, un réactif organométallique (tel qu'un acide boronique, un organozincique, un organomagnésien, un organostannane ou un organobismuthine), ainsi qu'un catalyseur de palladium, il est possible d'effectuer la formation de liens C–C. L'emploi d'acides boroniques comme source organométallique est de loin celle la plus commune, soit un couplage de Suzuki-Miyaura.[40] L'utilisation d'espèces organométalliques telles que des organozinciques, soit un couplage de Negishi, exige des conditions inertes, car ces réactifs sont sensibles à l'air et à l'humidité.[41] Similairement au couplage de Negishi, le couplage de Kumada-Corriu exige aussi des conditions inertes, car cette méthode de couplage-croisé emploie des réactifs organomagnésiens qui sont également sensibles à l'humidité.[42] L'utilisation d'organostannanes comme source organométallique, soit un couplage de Stille, fonctionne relativement bien pour effectuer des réactions de couplage-croisé, mais ces réactifs possèdent le désavantage d'avoir une haute toxicité.[43] Finalement, les organobismuthines sont une excellente alternative comme source organométallique, car ceux-ci ne sont pas toxiques, ils ne sont pas sensibles à l'air et l'humidité et les organobismuthines peuvent transférer leurs trois groupements organiques.

3.2. Formation de liens C–C via des couplages-croisés catalysés au palladium

Dans la littérature, il a été démontré que les organobismuthines sont capables d'effectuer des réactions de couplage-croisé sur toutes sortes de substrats tels que des chlorures d'acyle,[44] des halogénures allyliques et propargyliques,[45] des halogénures d'aryle (et d'hétéroaryle), (voir **Schéma 6**) etc.[46] En effet, Rao[47] a grandement contribué à l'approfondissement des connaissances des réactions de couplage-croisé catalysées au palladium impliquant des organobismuthines avec une grande variété de substrats.

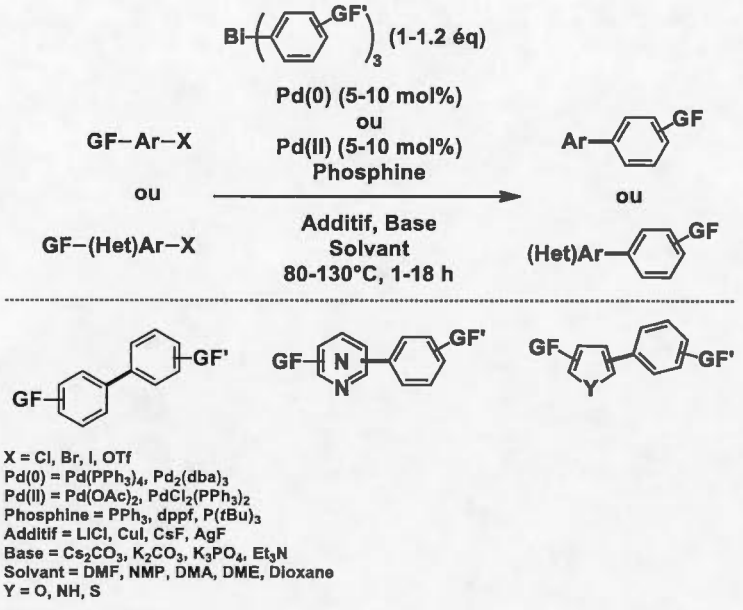


Schéma 6 : Couplages-croisés des halogénoaryles et d'halohétéroaryles avec des triarylbismuthines catalysés au palladium

En ce qui a trait au mécanisme des couplages-croisés catalysés au palladium, le Pd(0) perd premièrement deux ligands, L (voir étape **A**), pour passer d'un complèxe à 18 électron à un complexe à 14 électrons permettant ainsi l'addition oxydante du palladium dans le lien Ar–X, oxydant ainsi le Pd(0) en Pd(II) (voir étape **B**). Par la suite, on observe l'étape de la transmétallation où il y a un transfert d'aryle provenant de l'espèce organométallique sur le Pd(II) (voir étape **C**). Finalement, il y a élimination réductrice qui permet la formation du produit désiré, régénérant ainsi la source de Pd(0), ce qui ferme le cycle catalytique (voir étape **D**) (voir **Schéma 7**).[27] Il est à noter que le Pd(0) peut être généré *in situ* en réduisant du Pd(II) (typiquement $Pd(OAc)_2$) en Pd(0) par une phosphine (PPh_3 par exemple). En ajout, en catalyse au palladium, les trois aryles des triarylbismuthines peuvent être transférés lors d'une réaction de couplage-croisé, alors qu'en catalyse au cuivre, un seul aryle est transféré.

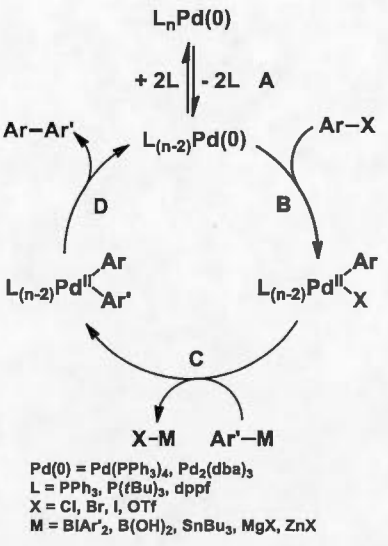


Schéma 7 : Mécanisme de la réaction de couplage-croisé d'halogénoaryle avec un triarylbismuthine (et d'autres sources organométalliques) catalysé au palladium

L'ajout de monoxyde de carbone dans le milieu réactionnel peut aussi mener à l'insertion de CO dans le lien Ar–Pd livrant ainsi des diarylcétones.[48]

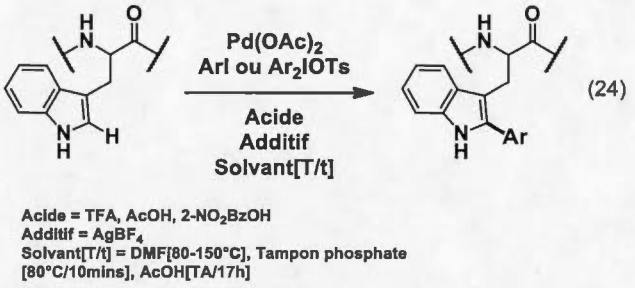
CHAPITRE IV
MODIFICATION D'ACIDES AMINÉS, DE PEPTIDES ET DE PROTÉINES

4.1. Modification d'acides aminés

4.1.1. Activation C–H

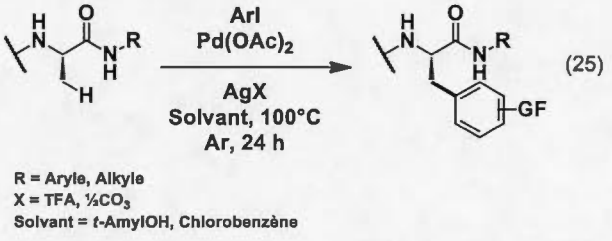
Dans la littérature, certains laboratoires ont développé des méthodologies permettant l'arylation de résidus d'acides aminés via l'activation d'un lien C–H, notamment sur le tryptophane[49] et l'alanine[50].

Dans le cas des activations C–H du tryptophane, ces réactions utilisent des iodures d'aryle ou des sels de diaryliodonium et elles sont catalysées au Pd(II), soit par le $Pd(OAc)_2$. L'activation C–H en position C-2 peut être effectuée soit dans un solvant organique, soit en milieu aqueux (tampon phosphate salin). Également, l'activation C–H du tryptophane peut être effectuée à température ambiante, ainsi que par microonde. La réaction performée à température ambiante requiert un plus long temps de réaction, soit 17 h, alors qu'un chauffage entre 80-150°C par microonde accélère cette réaction de façon drastique et celle-ci est complète après 5-20 minutes (voir **Éq 24**). De plus, cette réaction est très chimiosélective en présence d'une variété d'acides aminés. Cependant, cette méthodologie ne fonctionne pas sur des peptides contenant des résidus d'acides aminés ayant un atome de soufre tel que la méthionine, notamment en raison de la forte affinité entre le palladium et le soufre (acide mou et base molle).



Éq 24 : Activation C–H de la position C-2 du tryptophane avec des iodures d'aryles catalysé au $Pd(OAc)_2$

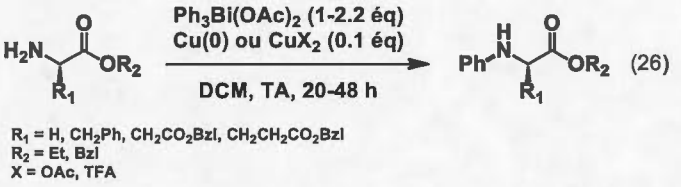
Dans le cas de l'activation C–H de l'alanine, encore une fois, celle-ci utilise toujours du $Pd(OAc)_2$, des iodures d'aryle et un sel d'argent afin d'effectuer l'arylation du CH_3 de sa chaîne latérale (voir **Éq 25**).



Éq 25 : Activation C–H du CH_3 de l'alanine avec des iodure d'aryles catalysé au $Pd(OAc)_2$

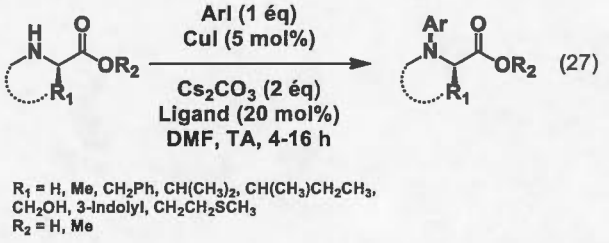
4.1.2. Arylation du N-terminal d'acides aminés

Les groupes de Barton[51] et Jain[52] ont rapporté des méthodologies pour aryler le N-terminal de certains acides aminés par catalyse au cuivre. Le groupe de Barton a employé des organobismuthines pentavalents comme source d'aryle par catalyse au Cu(0) ou au Cu(II) (voir **Éq 26**).



Éq 26 : Arylation du N-terminal d'acides aminés avec des organobismuthines pentavalents par catalyse au Cu(0) et au Cu(II)

Le groupe de Jain a utilisé des conditions de Buchwald pour effectuer l'arylation du N-terminal des acides aminés. Ils utilisent des iodures d'aryle comme source d'aryle, un catalyseur de Cu(I), ainsi qu'un ligand de type 1,3-dicétone (voir **Éq 27**).



Éq 27 : Arylation du N-terminal d'acides aminés avec des iodures d'aryles catalysé au Cu(I)

4.1.3. Arylation de chaînes latérales d'acides aminés par catalyse au cuivre

Certains groupes de recherche ont rapporté des méthodes d'arylation des chaînes latérales d'acides aminés avec l'emploi d'acides boroniques et de trifluoroborates de potassium comme source d'aryle par catalyse au Cu(II).

Notamment, le groupe de Molander[53] a effectué le transfert d'une varitété d'aryles sur l'hydroxyle de la sérine et de la thréonine (N- et C-terminal protégés). De plus, il a réussi à aryler de façon chimiosélective l'alcool de la sérine du dipeptide Cbz-

Ser-Thr-OMe avec un rendement de 22%. En outre, il démontre aussi un exemple d'arylation de tyrosine avec un rendement moyen de 42% (voir **Schéma 8**).

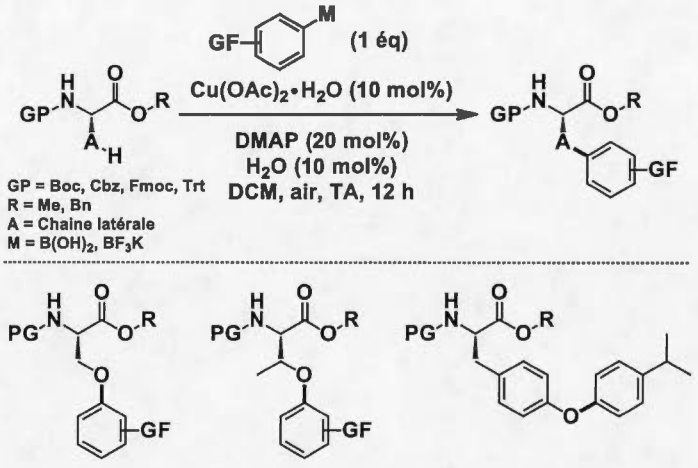
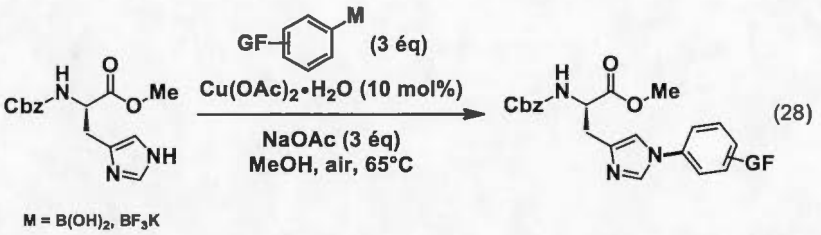


Schéma 8 : Arylation de sérine, thréonine et tyrosine par couplage de type Chan-Evans-Lam

De plus, le groupe de Campagne[54] a développé une méthode permettant l'arylation de la fonction imidazole de l'histidine en utilisant une variété d'acides boroniques et de trifluoroborates de potassium par catalyse au Cu(II). Or, ce groupe de recherche n'a arylé que des histidines N- et C-protégés contrairement à des substrats un peu plus complexes tels que des oligopeptides contenant plus d'un acide aminé (voir **Éq 28**). Le groupe de Hanzlik a rapporté une méthode d'arylation de l'histidine utilisant des iodures d'aryles par catalyse au Cu(II)[55] et plusieurs exemples d'arylation de l'histidine où ils utilisent des organoplombs ($ArPb(OAc)_3$) comme source d'aryle par catalyse au Cu(II) sont aussi décrits.[56]

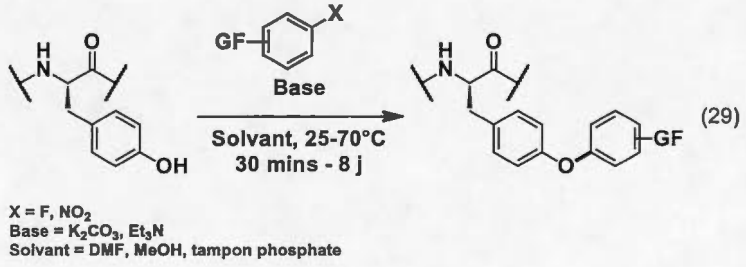


Éq 28 : Arylation d'histidine par couplage de type Chan-Evans-Lam

4.2. Arylation de la tyrosine

4.2.1. Substitution nucléophile aromatique (S_NAr)

Une des méthodes d'arylation du phénol de la tyrosine couramment utilisée est par substitution nucléophile aromatique (S_NAr) de groupes tels que F[57] et NO_2.[58] Il est important de savoir que les réactions de S_NAr se déroulent plus facilement en appauvrissant le cycle aromatique de sa densité électronique. En absence de groupes électroattracteurs, notamment NO_2, cette réaction peut prendre plusieurs jours, mais en présence de plusieurs groupes électroattracteurs, la réaction peut être complète après seulement 30 minutes (voir **Éq 29**).



Éq 29 : Substitution nucléophile aromatique de F et de NO_2 par la fonction phénol de la tyrosine

D'autre part, il est aussi possible d'effectuer une S_NAr sur un chlorure d'aryle via la formation d'un complexe métal-arène avec des métaux tels que Mn(I),[59] Fe(II)[60] ou Ru(II) (voir **Schéma 9**).[60b,61]

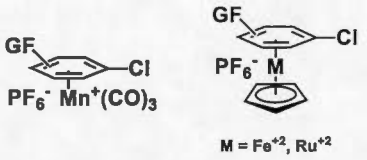
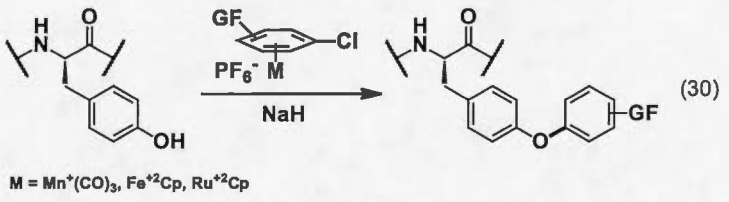


Schéma 9 : Formation de complexes métal-arène à base de Mn(I), Fe(II) ou Ru(II) et de chlorures d'aryle

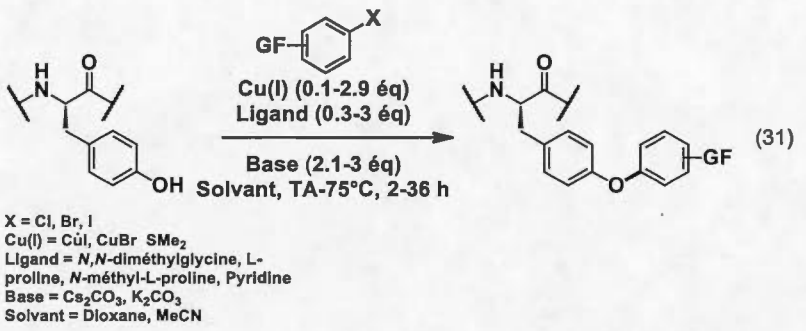
Parallèlement, le cycle aromatique est appauvrit en électrons ce qui permet la substitution du chlorure par la fonction phénol de la tyrosine. Après la formation des complexes illustrés au **Schéma 9**, ceux-ci peuvent être employés pour aryler la tyrosine, souvent après la déprotonation de la fonction phénol (voir **Éq 30**).



Éq 30 : Arylation de la tyrosine par S_NAr via la formation d'un complexe métal-arène à base de Mn(I), Fe(II) ou Ru(II)

4.2.2. Arylation catalysée au Cu(I)

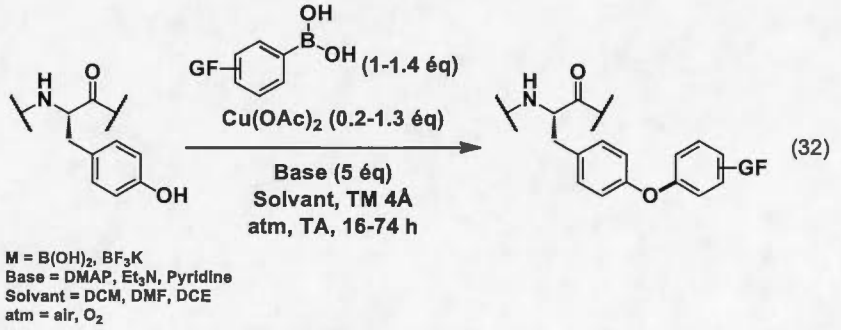
La méthodologie développée par Buchwald a été utilisée pour effectuer l'arylation de la fonction phénol de la tyrosine, soit en utilisant des halogénures d'aryles avec l'ajout d'une base, un ligand, ainsi qu'un catalyseur de Cu(I) (voir **Éq 31**). Ce couplage-croisé fonctionne mieux en utilisant des iodures d'aryles comme source d'aryle (versus ses homologues chlorés et bromés), car la réaction d'addition oxydante dans la liaison C–X se fait mieux avec les iodures. D'autre part, les ligands les plus employés dans ce type de réaction sont à base d'acides aminés, soient la *N,N*-diméthylglycine, la L-proline, ainsi que son dérivé protégé, la *N*-méthyl-L-proline.[62]



Éq 31 : Arylation de la tyrosine via un couplage de type Buchwald catalysé au Cu(I)

4.2.3. Arylation catalysée au Cu(II)

Certains laboratoires ont rapporté l'arylation de la tyrosine en effectuant un couplage-croisé de type Chan-Evans-Lam. Ces derniers ont effectué l'arylation par catalyse au Cu(II), soit le $Cu(OAc)_2$, en utilisant des acides boroniques ($ArB(OH)_2$) comme source d'aryle et des bases azotées telles que la DMAP, la Et_3N et la pyridine (voir **Éq 32**).[63] Cette réaction est effectuée à température ambiante et pour être en mesure d'utiliser une quantité substœchiométrique de cuivre, une atmosphère d'O_2 peut être employée. Cependant, au meilleur de nos connaissances, aucun laboratoire n'a rapporté l'arylation de la tyrosine en employant des triarylbismuthines comme source d'aryle.



Éq 32 : Arylation de la tyrosine via un couplage de type Chan-Evans-Lam catalysé au cuivre

4.2.4. Arylation catalysée au Pd(0)

Willis et Frost[64] ont publié un article très intéressant où ils se concentrent sur l'arylation chimiosélective de trois acides aminés, soient la tyrosine, la déhydroalanine (dhAla) et le tryptophane. L'arylation de la tyrosine a été effectuée en utilisant une source de Pd(0), à savoir le $Pd_2(dba)_3$, une phosphine (*t*Bu-X-phos) au départ d'un bromure d'aryle comme source d'aryle. L'arylation de la déhydroalanine a été effectuée par un addition conjuguée catalysée au Rh(acac)(C_2H_4) avec du *rac*-BINAP et un acide boronique comme source d'aryle. L'arylation du tryptophane a été effectuée en utilisant du $Pd(OAc)_2$ comme catalyseur, la Xantphos comme ligand et un bromure d'aryle comme source d'aryle. L'arylation conjuguée sur la déhydroalanine, ainsi que l'arylation du tryptophane ont procédé de façon chimiosélective avec des rendements de 54% et 71% respectivement. Or, dans le cas de la tyrosine, la réaction a donné un rendement de 48% d'*O*-arylation et 13% de N-arylation. Cela étant dit, les méthodes d'arylation de tryptophane et d'addition conjuguée sur la déhydroalanine sont chimiospécifiques alors que l'arylation de la tyrosine est chimiosélective (voir **Schéma 10**).

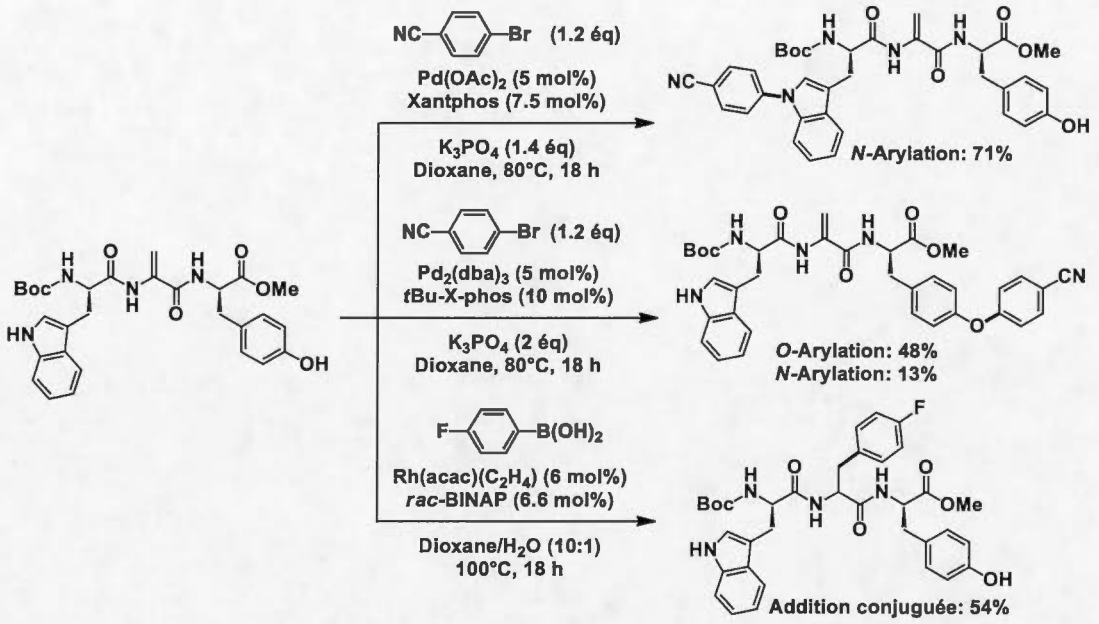
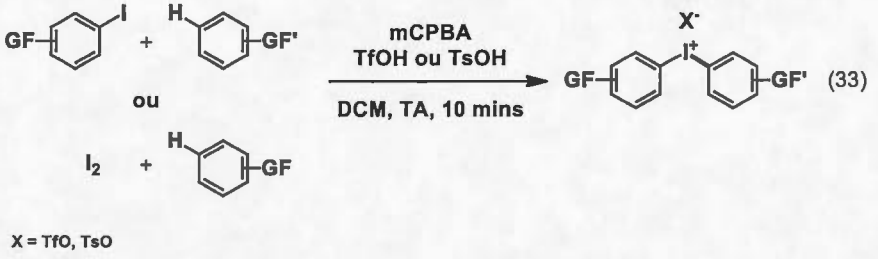


Schéma 10 : Arylation chimiosélective de tryptophane, déhydroalanine et tyrosine via couplage-croisé au Pd(II), addition conjuguée catalysée au Rh(I) et couplage-croisé catalysé au Pd(0) respectivement

4.2.5. Iode hypervalent

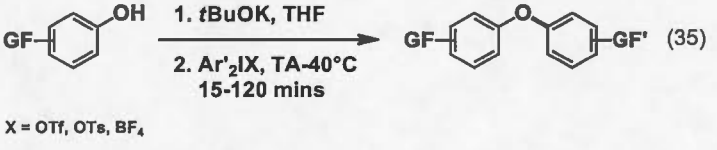
En outre, le groupe d'Olofsson[65] a rapporté une méthode d'arylation de la tyrosine via la formation de sels de diaryliodonium, soit une méthode qui ne requiert pas l'emploi de métaux. Le sel de diaryiodonium peut être formé en mélangeant un iodure d'aryle et un aryle quelconque (ou un aryle avec du I_2) et en rajoutant un oxydant, soit mCPBA, en présence d'acide tel que TfOH, TsOH (voir **Éq 33**). Ce dernier peut aussi être synthétisé à partir d'un iodure d'aryle, un oxydant et un acide boronique (voir **Éq 34**).



Éq 33 : Préparation de sels de diaryliodonium par emploi d'iodures d'aryles (ou d'I_2) et un aryle quelconque en présence d'un oxydant

Éq 34 : Préparation de sels de diaryliodonium par emploi d'iodures d'aryles, un oxydant et d'un acide boronique

Une fois que les sels de diaryliodonium sont préparés, ils peuvent être utilisés dans une réaction d'arylation de phénols (incluant deux exemples d'arylation de la tyrosine) (voir **Éq 35**).



Éq 35 : Arylation de phénols en utilisant des sels de diaryliodonium comme source d'aryle

4.3. Marquage d'acides aminés sur des protéines

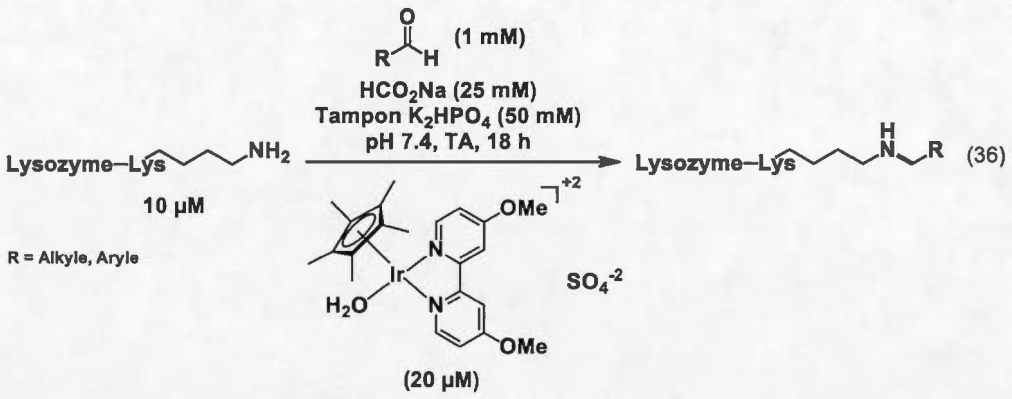
Certains groupes de recherche ont été en mesure de développer des méthodologies pour marquer des acides aminés spécifiques sur des protéines tels que la lysine, le tryptophane, la tyrosine et la cystéine. Par la suite, les modifications

effectuées sur les protéines peuvent être détectées par des techniques analytiques telles que la SMHR (par ajout d'un fragment sur la protéine ou par ajout d'atomes avec une abondance isotopique intéressante telle que le Cl et le Br), la RMN (par marquage isotopique au ^{2}D, ^{13}C ou en ajoutant du fluor) ou encore la spectrométrie de fluorescence (en ajoutant des sondes fluorophores).

Dans la littérature, on retrouve plusieurs méthodes de modification de protéines.[66] Seulement quelques-unes entre elles seront présentés dans les sections qui suivent.

4.3.1. Modification de la lysine

En ce qui concerne la modification de la lysine, une des stratégies employées est l'amination réductrice de sa fonction amine avec un aldéhyde ou une cétone. Il est possible d'effectuer cette réaction en utilisant le cyanoborohydrure de sodium ($NaBH_3CN$) comme réducteur. Cependant, cette méthode nécessite l'utilisation d'un grand excès de réducteur ce qui entraîne la dénaturation de la protéine qui peut être toxique pour des cellules vivantes.[67] Pour contourner ce problème, le groupe de Francis[68] a développé une méthode d'amination réductrice la lysine du lysozyme catalysée à l'iridium en utilisant du formiate de sodium comme source d'hydrure (voir **Éq 36**). En effet, le formiate de sodium forme un hydrure (et un dégagement de CO_2) qui vient substituer la molécule d'eau sur l'Ir(I) menant ainsi au complexe actif dans cette réaction. Après l'addition des fragments d'amination réductrice sur les résidus de lysine, ces modifications peuvent être détectées par spectrométrie de masse où on peut voir un signal qui correspond à chaque amination réductrice effectuée sur la même protéine ($Mm + xn^{+}$; ou Mm = masse molaire de la protéine, x = masse molaire du fragment ajouté, n = nombre entier (0, 1, 2, 3)).

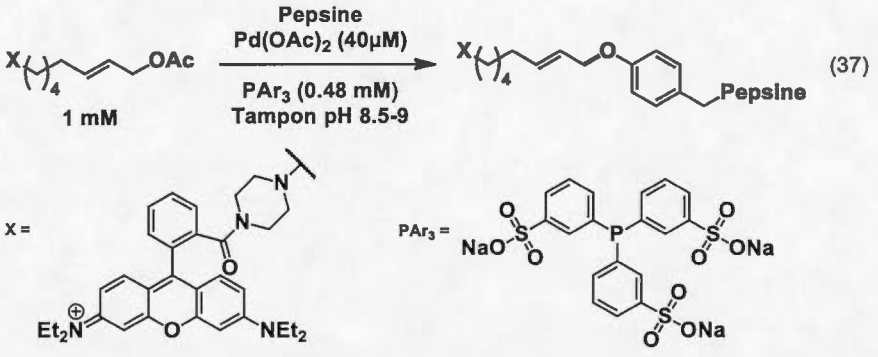


Éq 36 : Amination réductrice de la lysine du lysozyme en utilisant du formiate de sodium par catalyse à l'Ir(I)

4.3.2. Modification de la tyrosine

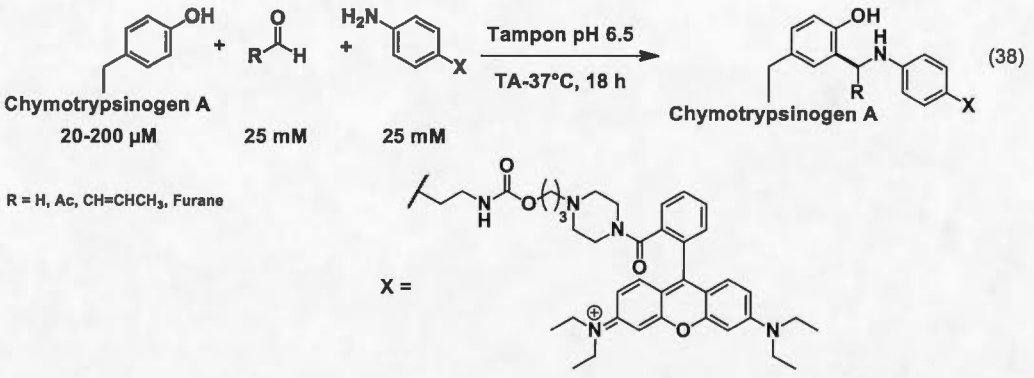
En ce qui a trait au marquage de la tyrosine, le groupe de Francis a été en mesure de modifier ce résidu de façon chimiosélective par deux méthodes différentes, soit via une réaction de Tsuji-Trost avec un acétate allylique par catalyse au Pd(0) ou soit via une réaction de type Mannich en rajoutant une aniline et un aldéhyde (le phénol est considéré comme un énol).

En ce qui concerne la réaction de Tsuji-Trost, cette réaction utilise du $Pd(OAc)_2$ comme source de palladium avec du triphenylphosphine tris-sulfonate (cette phosphine est soluble en milieu aqueux et elle génère du Pd(0) à partir du Pd(II)) dans un tampon phosphate (pH : 8.5-9). Cette réaction est très rapide et elle permet de transférer un acétate allylique comprenant une rhodamine, c'est-à-dire un fluorophore. En effet, ce groupe a été capable d'alkyler certains résidus de tyrosine sur la pepsine (plus particulièrement Y171). Le groupe de Francis a aussi été en mesure de prouver que l'alkylation a eu lieu sur la tyrosine en effectuant une digestion protéolytique de la pepsine alkylée (voir **Éq 37**).[69]



Éq 37 : Alkylation de type Tsuji-Trost d'un résidu de tyrosine sur une protéine avec un acétate allylique comprenant une rhodamine fluorescente

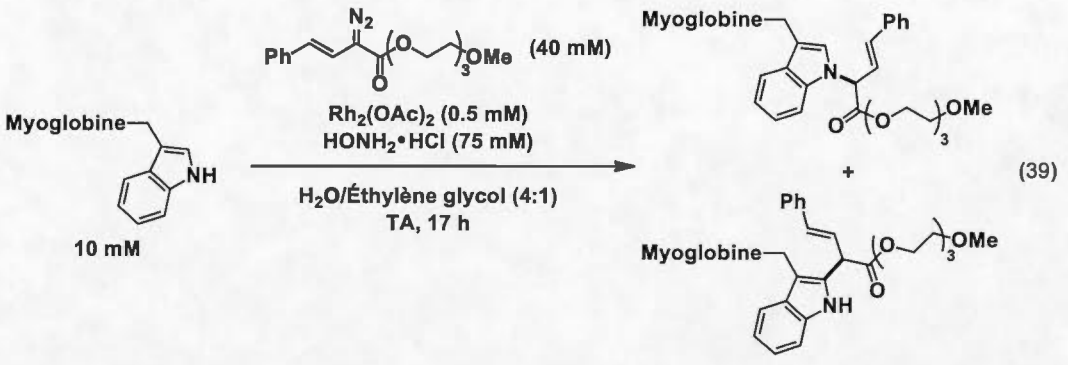
En ce qui touche la réaction de Mannich, cette réaction est effectuée dans un tampon phosphate de pH 6.5 (légèrement acide pour former l'iminium qui sera attaqué par le carbone en alpha du phénol). Cette méthode est surtout intéressante car elle est effectuée en milieu aqueux, elle ne nécessite pas de catalyseur métallique et elle est sélective pour la tyrosine. De plus, cette approche de marquage de la tyrosine permet aussi l'addition d'une sonde fluorescente telle que la rhodamine illustrée ci-dessous (voir **Éq 38**). Après la réaction, la protéine modifiée a été sujet à une digestion protéolytique qui a permis de déterminer que la réaction a bel et bien pris place sur le résidu de tyrosine, plus particulièrement Y146 et Y171 (les autres résidus de tyrosine sont significativement moins accessibles et il est présumé qu'ils ne réagissent pas), en effectuant un analyse MALDI-MS.[70]



Éq 38 : Marquage de résidus de tyrosine avec une rhodamine sur la Chymotrypsinogen A par réaction de Mannich

4.3.3. Modification du tryptophane

Toujours dans l'optique de la modification de protéines, le groupe de Francis a développé une méthode pour alkyler la tyrosine sur la myoglobine de façon sélective en utilisant des carbénoïdes de rhodium et de l'hydroxylamine en milieu aqueux. Il est à noter que l'alkylation peut livrer le produit de *N*-alkylation ou de *C*-alkylation en position C-2 du tryptophane (voir **Éq 39**). Ce phénomène a été élucidé en effectuant la réaction d'alkylation sur un substrat plus simple, soit le 3-méthylindole. Pour prouver que l'alkylation a pris place sur le tryptophane, une digestion protéolytique a été effectuée et il a été déterminé que la réaction d'alkylation a eu lieu sur les résidus de tryptophane W7 et W14 en analysant par spectrométrie de masse (ionisation par électronébuliseur).[71]

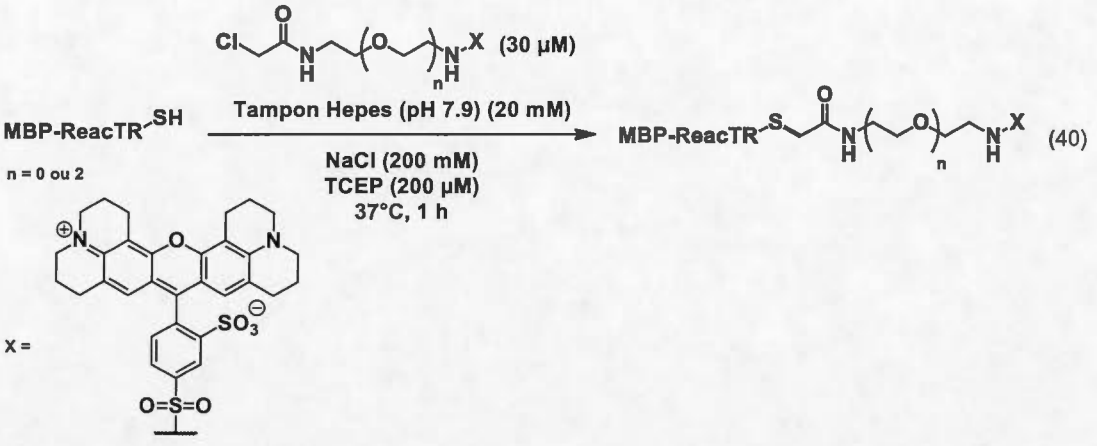


(39)

Éq 39 : Marquage de résidus de tryptophane sur la myoglobine par addition de carbénoïdes de rhodium

4.3.4. Modification de la cystéine

Depuis l'année 1935, les iodoacétamides ont été employés pour modifier et étudier les résidus de cystéine présents sur les protéines, notamment la kératine.[72] Or, il s'avère que la lysine était aussi capable de substituer l'iode de l'iodoacétamide. Conséquemment, les chloroacétamides sont plus fréquemment utilisés, car ils sont plus sélectifs pour l'alkylation de la cystéine.[73] À cet égard, le groupe de Jäschke a utilisé des chloroacétamides comportant une sonde fluorophore (TexasRed) afin de marquer la cystéine sur la protéine MBP-ReacTR (voir **Éq 40**).[74]



Éq 40 : Marquage de résidus cystéines sur la protéine MBP-ReacTR par addition d'un chloroacétamide comprenant une sonde fluorophore (TexasRed)

CONCLUSION

Pour conclure, nous avons été en mesure d'établir que l'utilisation des triarylbismuthines fonctionnalisés comme source d'aryle est très efficace pour effectuer des couplages-croisés catalysés au palladium ou au cuivre. Ces réactifs possèdent une faible toxicité et sont stables à l'air et à l'eau. De plus, les réactifs d'organobismuth sont capables de tolérer toutes sortes de groupes fonctionnels et de conditions (acide ou basique). Ces derniers peuvent également tolérer la présence de nucléophiles ainsi que des oxydants et des réducteurs. Afin d'obtenir des triarylbismuthines hautement fonctionnalisés, nous avons été capable d'effectuer la dérivatisation des groupes fonctionnels présents sur ces derniers.

L'obtention des structures rayons X de certains organobismuthines nous a permis de visualiser l'effet de la position et la nature des substituants sur la structure de ces derniers. Notamment, en présence d'atomes donneurs, tel que l'oxygène, sur des organobismuthines substitués en *ortho*, il peut y avoir un interaction entre l'atome donneur et le bismuth (tel qu'illustré par les structures rayons X que nous avons obtenues).

Les organobismuthines peuvent être utilisés pour aryler toutes sortes de substrats via des couplages-croisés catalysés au palladium (pour former des liens C–C) à partir d'halogénures d'aryle et au cuivre (pour former des liens C–N, C–O et C–S) à partir de nucléophiles de type N–H, O–H et S–H.

En ce qui concerne les couplages-croisés catalysés au palladium, nous avons déterminé que l'ajout de LiCl ou de CuI en tant qu'additif et l'emploi de bases telles que Cs_2CO_3, K_3PO_4 et Rb_2CO_3 était bénéfique pour le rendement de la réaction. De plus, les couplages-croisés catalysés au palladium ont l'avantage d'être capable de transférer leurs trois groupes organiques.

En ce qui concerne les couplages-croisés catalysés au cuivre, nous avons été en mesure d'aryler une grande variété de substrats, notamment des hétérocycles azotés, des phénols, des aminoalcools, etc.

Compte tenu de ceci, nous avons transposé nos méthodes à l'arylation d'acides aminés. Nous avons effectué l'arylation de la tyrosine, la cystéine, l'histidine, le tryptophane, la sérine, la lysine, la glutamine, la thréonine et l'acide glutamique. En somme, nous avons déterminé que notre méthode d'arylation démontrait une certaine sélectivité envers l'arylation de la tyrosine. Par la suite, nous avons démontré que nous étions capables de transférer une grande variété d'aryles sur un tripeptide contenant un résidu de tyrosine. En fait, nous avons pu aryler la tyrosine avec des aryles portant soit un atome de chlore ou de brome, ce qui pourrait être très utile pour marquer ce résidu dans des peptides afin de le suivre à travers de processus biochimiques en utilisant des techniques analytiques telle que la MSHR. Finalement, nous avons pu aryler la tyrosine de façon chimiosélective sur un dipeptide contenant à la fois la tyrosine et le tryptophane.

Malgré le fait qu'en catalyse au cuivre, les organobismuthines ne peuvent transférer qu'un aryle sur trois, cette méthode est très puissante et permet l'arylation d'une panoplie de substrats de type N–H, O–H et S–H. Ces types de couplages-croisés peuvent aussi être effectués en utilisant des acides boroniques comme source d'aryle par catalyse au cuivre (couplage de type Chan-Evans-Lam), mais il est important de considérer l'emploi d'organobismuthines comme une méthode alternative afin d'effectuer des couplages qui seraient difficiles en utilisant les acides boroniques.

ANNEXE A
CONTRIBUTIONS SCIENTIFIQUES

Article 1 : Synthesis of Highly Functionnalized Triarybismuthines by Functional Group Manipulation and Use in Palladium- and Copper-Catalyzed Arylation Reactions

Hébert, M.; Petiot, P.; Benoit, E.; Dansereau, J.; Ahmad, T.; Le Roch, A.; Ottenwaelder, X.; Gagnon, A. *J. Org. Chem.* **2016**, *81*, 5401-5416.

Mise en Contexte

Au cours des dernières années, notre groupe a développé des méthodologies nous permettant de former des liaisons C–C, par catalyse au palladium, et des liaisons C–O et C–N, par catalyse au cuivre, en utilisant des triarylbismuthines fonctionnalisés. Étant donné que la synthèse des organobismuthines implique l'ajout d'une espèce organométallique (organomagnésien, organolithien, organozinzique, etc.) sur un sel de bismuth (typiquement $BiCl_3$), certains groupes fonctionnels sensibles aux nucléophiles (aldéhyde, cétone, ester, etc.) ou aux bases fortes (protons acides de type N–H, O–H, S–H) ne peuvent pas être présents sur l'espèce organométallique. Dans cette optique, nous avons été en mesure d'effectuer une manipulation de groupes fonctionnels directement sur les organobismuthines afin d'obtenir des dérivés hautement fonctionnalisés.

Dans la littérature, lors des réactions de couplages-croisés catalysés au palladium, on emploie souvent des acides boroniques ou des organostannanes comme source organométallique. Cependant, en raison de leur toxicité, les organostannanes

sont de moins en moins utilisés. Par conséquent, les organobismuthines sont une excellente alternative aux acides boroniques pour les réactions de couplage difficiles.

En ce qui concerne les couplages-croisés catalysés au cuivre, encore une fois, les acides boroniques sont souvent utilisés dans des réactions de type Chan-Evans-Lam. Cependant, il s'avère que les organobismuthines donnent des résultats comparables ou supérieurs à ceux obtenus avec les acides boroniques. D'où l'intérêt d'investiguer leur efficacité à transférer des aryles hautement fonctionnalisés sur des subtrats de type N–H et O–H.

Contributions personnelles

La synthèse des organobismuthines hautement fonctionnalisés employés dans les réactions de couplage-croisé est une de mes contributions pour cet article. Notamment, j'ai effectué la synthèse de **1a**, **1d**, **1m**, **1n**, **1o** (**Scheme 3**) **1s**, **1t**, **21a**, **21b**, **21c** (**eqs 1-5**), **21d**, **21e**, **21f**, **21g** (**Scheme 4**) et **21h** (**Scheme 5**). De plus, j'ai cristallisé les organobismuthines **1s**, **1t** et **21e** afin d'obtenir les structures rayons X (**Figure 1**).

En ajout, j'ai effectué des couplages-croisés catalysés au cuivre avec l'emploi de triarylbismuthines trivalents et pentavalents. En effet, j'ai synthétisé les produits **17a**, **34a**, **34c**, **34d**, **35b** (**Scheme 6**), **37a**, **37b** (**Scheme 7**) et **37e** (**Table 4**).

Finalement, j'ai participé à la rédaction de l'article et j'ai préparé la partie expérimentale.

Contributions des coauteurs

Pauline Petiot a également effectué la synthèse d'organobismuthines et elle a préparé la majorité des composés de la **Table 1** et la moitié de la **Table 2**. Elle a aussi préparé le **Scheme 9**.

Emeline Benoit a complété la **Table 1** et elle a fait un quart de la **Table 2**.

Julien Dansereau a complété un quart de la **Table 1**, la moitié du **Scheme 6** et a préparé la **Table 3**.

Tabinda Ahmad a préparé la majorité du Scheme 7 et elle a recristallisé les organobismuthines **1f**, **1i**, **1k**, **1n**, et **21c** afin d'avoir les structures rayons X.

Adrien Le Roch a effectué la repurification de certains produits impurs.

Xavier Ottenwaelder a effectué les analyses par rayons X.

Alexandre Gagnon était le chef d'équipe pour les expériences et les analyses effectuées. Il était également en charge de la recherche bibliographique et de la rédaction de l'article.

Manuscript 2: Chemoselective Copper-Catalyzed *O*-Arylation of Small Tyrosine-Containing Peptides using Functionnalized Organobismuth Reagents

Hébert, M.; Le Roch, A.; Archambault, M.-J.; Pinsonneault, F.; Lachance, H.; Gagnon, A. *Org. Lett.* **2016**, (En préparation)

Mise en contexte

Depuis 2014, le groupe du Pr. Gagnon a utilisé des triarylbismuthines fonctionnalisés pour effectuer de réactions de couplage-croisé catalysées au cuivre afin de former des liaisons C–O et C–N. Les indoles, les imidazoles, les phénols et les aminoalcools sont quelques exemples de substrats arylés en utilisant cette méthodologie. Étant donné que ces groupes fonctionnels se retrouvent sur les chaînes latérales des acides aminés, notamment le tryptophane, l'histidine, la tyrosine, la sérine et la thréonine, cette méthodologie a été transposée à l'arylation d'acides aminés et de peptides.

La modification des chaînes latérales d'acides aminés peut s'avérer très utile en chimie médicinale ou en biochimie. En effet, plusieurs médicaments possèdent des motifs d'acides aminés dans leur structure. En biochimie, il peut être utile de marquer certains acides aminés dans des peptides ou des protéines pour être en mesure de les suivre avec des techniques analytiques à travers de des processus biochimiques.

Dans la littérature, les méthodes d'arylation des chaînes latérales d'acides aminés qu'on retrouve sont surtout par catalyse au Cu(I) avec des halogénures d'aryles ou au Cu(II) utilisant des acides boroniques ou des trifluoroborates de potassium. Or, l'utilisation des organobismuthines pour l'arylation des chaînes latérales des acides aminés n'a toujours pas été rapportée dans la littérature (hormis l'arylation du tryptophane par le groupe de Gagnon).

Contributions personnelles

La synthèse des organobismuthines hautement fonctionnalisés employés dans les réactions de couplage-croisé est une de mes contributions pour cet article. Notamment, j'ai effectué la synthèse des organobismuthines **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **6i**, **6j**, **6k**, **6l**, **6m**, **6n**, **6o**, **6p**, **6q**, **6r**, **6s** et **6t** (**Scheme 5**). Ensuite, j'ai effectué l'arylation des acides aminés **11a** **11b**, **11d**, **11e**, **11f**, **11h** et **11i** (**Scheme 3**). Par la suite, j'ai synthétisé les tripeptides **12**, **13** et **15** (**Scheme 4**). Par après, j'ai préparé les tripeptides arylés **16a**, **17**, **18a**, **18b** et **19** (**Scheme 4**). J'ai effectué la table d'optimisation illustrée à la **Table 1**. De plus, j'ai effectué les arylations des tripeptides **16b**, **16c**, **16d**, **16e**, **16g**, **16h**, **16i**, **16j**, **16k**, **16l**, **16m**, **16n**, **16o**, **16p**, **16q** et **16r** (**Scheme 5**). En ajout, j'ai préparé le dipeptide **23** (**Scheme 6**).

Finalement, j'ai participé à la rédaction de l'article et j'ai préparé la partie expérimentale.

Contributions des coauteurs

Adrien Le Roch a préparé le composé **11c**, il a fait un quart du **Scheme 5** et il a fait le **Scheme 6**. Il a également effectué la synthèse des peptides **12** et **20**.

Marie-Jeanne Archambault a effectué la synthèse des composés **11f**, **11g** et elle a effectué la synthèse des peptides **14** et **15**.

Francis Pinsonneault a commencé le projet d'arylation des acides aminés en testant plusieurs conditions de réaction qui se retrouvent dans la table d'optimisation (**Table 1**).

Hugo Lachance est celui qui a eu l'idée pour le projet d'arylation des acides aminés.

Alexandre Gagnon était le chef d'équipe pour les expériences et les analyses effectuées. Il a aussi fait la recherche bibliographique et la rédaction de l'article.

ANNEXE B

Article 1 : Synthesis of Highly Functionnalized Triarybismuthines by Functional Group Manipulation and Use in Palladium- and Copper-Catalyzed Arylation Reactions

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Synthesis of Highly Functionalized Triarylbismuthines by Functional Group Manipulation and Use in Palladium- and Copper-Catalyzed Arylation Reactions

Martin Hébert,[†] Pauline Petiot,[†] Emeline Benoit,[†] Julien Dansereau,[†] Tabinda Ahmad,[†] Adrien Le Roch,[†] Xavier Ottenwaelder,[‡] and Alexandre Gagnon*[,†]

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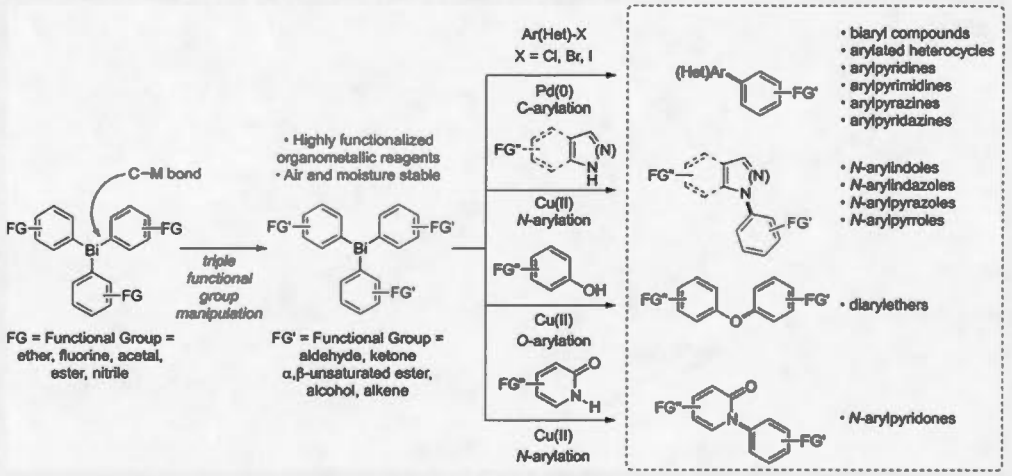
Supporting Information



ABSTRACT: Organobismuthines are an attractive class of organometallic reagents that can be accessed from inexpensive and nontoxic bismuth salts. Triarylbismuthines are particularly interesting due to their air and moisture stability and high functional group tolerance. We report herein a detailed study on the preparation of highly functionalized triarylbismuth reagents by triple functional group manipulation and their use in palladium- and copper-catalyzed *C*-, *N*-, and *O*-arylation reactions.

■ INTRODUCTION

Triarylbismuthines (also known as triarylbismuthanes) are a class of organometallic reagents that can be prepared from inexpensive and nontoxic bismuth salts.[1,2] These reagents are particularly attractive since they are air and moisture stable and can be purified by simple flash chromatography or crystallization. Moreover, organobismuth reagents are remarkably tolerant to numerous functional groups, making them highly suitable for methodology development.[3] They have also found applications in total synthesis,[4] in the preparation of transition metal complexes,[5] as catalysts for polymerization reactions,[6] and in medicinal chemistry.[7] Organobismuth reagents are divided into two main classes: trivalent and pentavalent organobismuthines, with bismuth in the +3 and +5 oxidation levels, respectively. Both classes have found applications in synthesis. For example, Barton and Finet reported in the 1980s a series of arylation reactions using triphenylbismuth and triphenylbismuth diacetate as arylating agents.[8] More recently, Rao greatly contributed to expanding the use of this class of reagents in organic synthesis and more specifically in palladium-catalyzed reactions.[9]

Our group has reported in recent years a portfolio of methods for the formation of C–C,[10] C–N,[11] and C–O[12] bonds using functionalized trivalent organobismuth reagents. These methods allow the transfer of functionalized aryl groups on scaffolds as diverse as pyridines **2**, pyrimidines **4**, pyrazines **6**, pyridazines **8**, indazoles and pyrazoles **10**, indoles and pyrroles **12**, phenols **14**, pyridones **16**, and 1,2-aminoalcohols **18**, providing access to a range of medicinally relevant compounds (Scheme 1). These methodologies operate under mild conditions and tolerate a wide variety of functional groups on both coupling partners.

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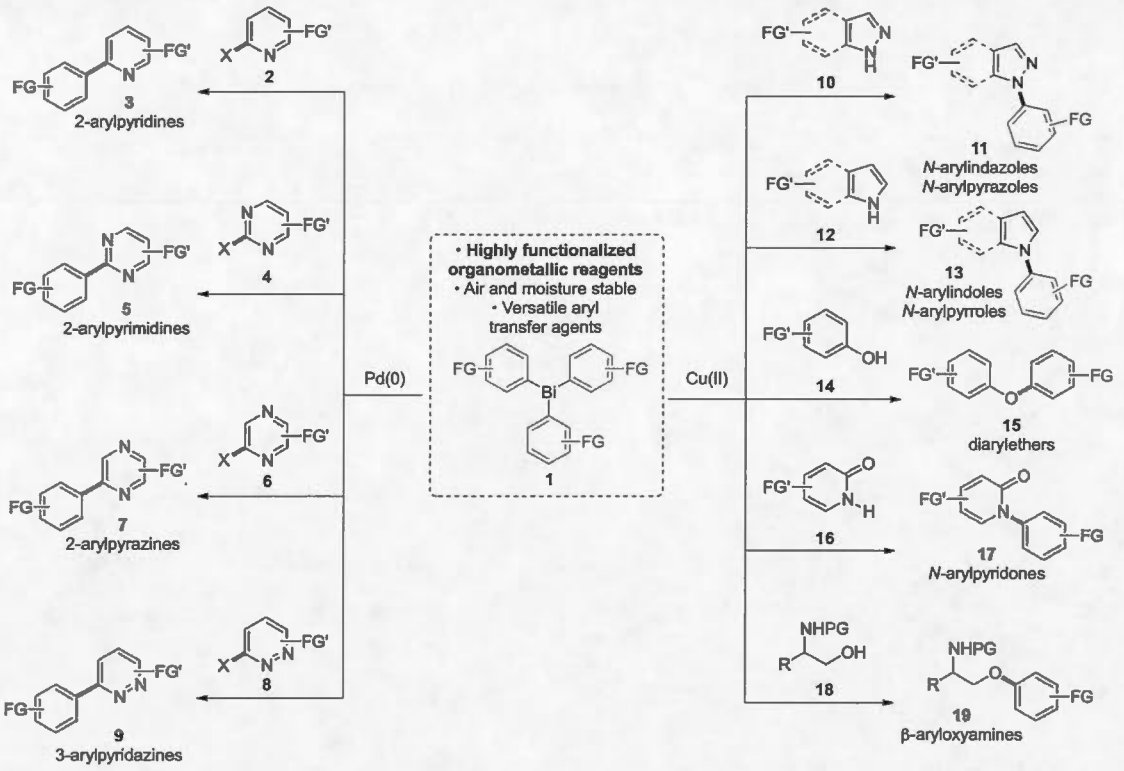
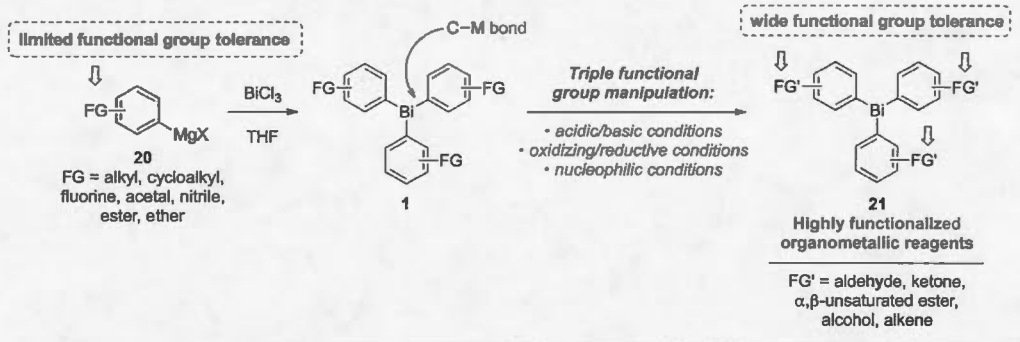
Scheme 1. Triarylbismuthines 1 in Arylation Reactions: Access to Highly Functionalized and Medicinally Relevant Compounds



Scheme 2. Synthesis of Highly Functionalized Organobismuthines 21 by Functional Group Manipulation Directly on Organometallic Species 1 (FG = Functional Group)



Triarylbismuth reagents **1** can be easily accessed via addition of Grignard reagents **20** onto bismuth chloride (Scheme 2). However, due to the high reactivity of organomagnesium reagents, organobismuthines bearing electrophilic or acidic functional groups cannot be synthesized directly using this approach. Condon reported an elegant and powerful method to prepare functionalized organobismuth reagents by the addition of organozinc reagents obtained from a cobalt–zinc metal–halogen exchange reaction on aryl halides.[13] While this method is quite general, groups bearing acidic protons such as alcohols cannot be introduced using this methodology. Therefore, alternative methods are still desirable to access highly functionalized organobismuthines. The strategy that we explored consists of introducing the incompatible functional group by performing a functional group transformation directly on the organobismuth species. In the course of our studies, we found that the C–Bi bond in organobismuthines is remarkably resistant to acidic, reductive, and even oxidative conditions, thus enabling the transformation of the functional group FG in **1** into a more elaborated functional group FG′ in **21** (Scheme 2). This reaction actually corresponds to a triple group manipulation on a single substrate. To be efficient, it therefore requires a high level of control of the reaction conditions since, to a first approximation, the overall yield is given by the cube of the yield-per-function. We report herein an extensive study on the successful preparation of highly functionalized triarylbismuth reagents using this approach and their use in palladium- and copper-catalyzed arylation reactions.

■ RESULTS AND DISCUSSION

a. Preparation of Triarylbismuthines. We began by synthesizing a set of substituted and unsubstituted organobismuthines **1a–r** bearing simple functional groups by adding organomagnesium reagents **20** to bismuth chloride (Scheme 3). The Grignard reagents **20** were prepared by reacting the corresponding aryl halides **22** with metallic magnesium at reflux of ether or THF. Using this approach, 18 different

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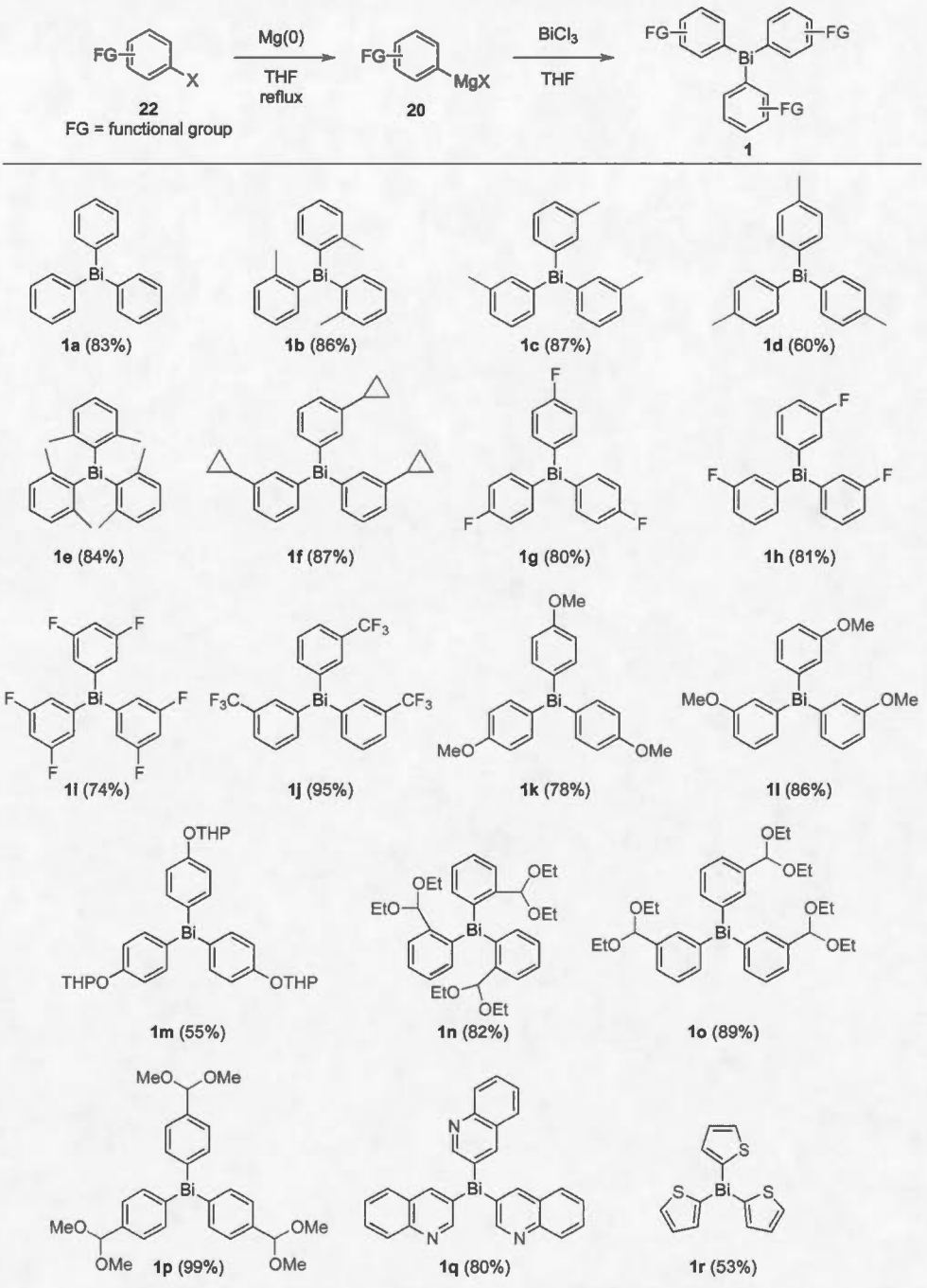
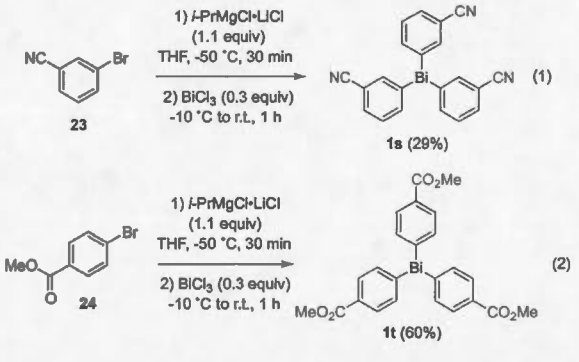
Scheme 3. Direct Preparation of Organobismuthines 1a–r by Addition of Organomagnesium Reagents 20 to Bismuth Chloride



unsubstituted and *ortho*, *meta*, and *para* substituted triaryl- and triheteroarylbismuthines were synthesized in 53% to 99% yields.

For the introduction of nitriles and esters, the required organomagnesium reagents were generated using Knochel's procedure.[14] Thus, addition of the isopropylmagnesium chloride lithium chloride complex onto 3-cyanobromobenzene **23** or methyl 4-bromobenzoate **24** at −50 °C afforded the corresponding Grignard reagents, which were then reacted with bismuth chloride to provide **1s** and **1t** in moderate yields (eqs 1 and 2).



To begin our exploration of functional group manipulation on organobismuthines, we added 6.0 equiv of methylmagne-

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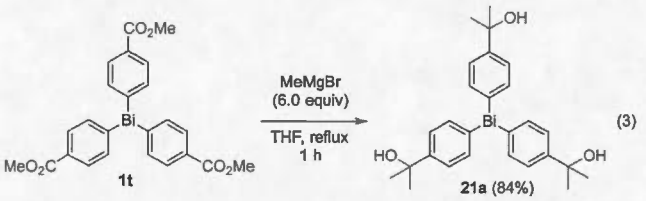
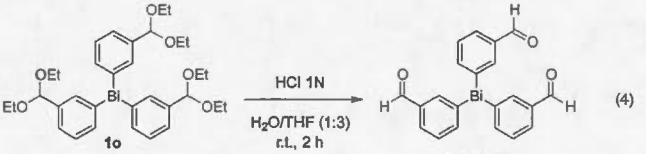
sium bromide on the ester derivative **1t**, affording **21a** in 84% yield (i.e., 94% yield per ester function) (eq 3). This simple



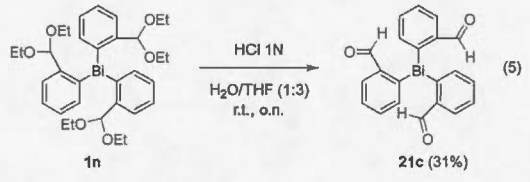
(3)

transformation demonstrates that the concept of functional group modification in the presence of a C–Bi bond is viable, giving us an impetus to explore other reactions directly on organobismuthines.

Due to their high electrophilicity, aldehydes cannot be present on organomagnesium reagents. Therefore, the preparation of organometallic reagents bearing aldehydes is only possible with less electropositive metals such as tin,[15] boron,[16] zinc,[17] or indium.[18] However, the toxic nature of tin greatly limits its use in synthesis. Although many organoboronic acids bearing aldehydes are commercially available, their use in metal-catalyzed reactions often requires extensive optimization of the reaction conditions. Conversely, arylzinc reagents possessing aldehydes have proved to be very useful in palladium-catalyzed cross-coupling reactions, but strictly anhydrous conditions are mandatory due to their high sensitivity to moisture. Finally, while organoindiums have generated great interest in the synthetic community over the past decade, the cost of indium greatly limits their application in synthesis. In this context, organobismuthines bearing aldehydes can fill an important need in organic synthesis. Starting from tris((3-diethoxymethyl)phenyl)bismuthine **1o**, we prepared the tris-formyl derivative **21b** in excellent yield by hydrolysis of the acetal function under acidic conditions (eq 4).



(4)



(5)

Surprisingly, using the same conditions on tris((2-diethoxymethyl)phenyl)bismuthine **1n** led to a much lower yield of the *ortho* analogue **21c** (eq 5). While this overall yield is low, it still corresponds to a 67% yield per acetal function. This example illustrates the need for very efficient conditions to get a satisfactory triple functional group modification.

We then took advantage of the versatility of the aldehyde function in **21b** to introduce other functional groups on the organobismuth species (Scheme 4). For example, addition of methylmagnesium bromide on **21b** provided tris(3-(1-hydroxyethyl)phenyl)bismuthine **21d** in quantitative yield. Reduction of the aldehyde function in **21b** was also accomplished using sodium borohydride, affording tris(3-(hydroxymethyl)phenyl)-bismuthine **21e** in 97% yield. An olefination reaction using Wittig conditions was then performed on **21b**, leading to the corresponding cinnamyl ester and vinyl derivatives **21f** and **21g** in 80% and 82% yield, respectively. These examples show that organobismuthines are resistant to organometallic and reductive reagents in addition to phosphorus ylides.

Next, we sought to introduce a ketone on the organobismuth reagent by oxidizing the secondary alcohol in **21d** (Scheme 5). Since trivalent organobismuthines can be oxidized into their pentavalent counterparts by oxidizing agents[19] and by hypervalent iodonium reagents,[8c,20] it was unclear if the bismuth(III) center would tolerate the oxidizing conditions required to oxidize the alcohol into the corresponding ketone. To our satisfaction, tris(methyl ketone) **21h** was obtained in acceptable yield using Dess-Martin periodinane **25**. Alternatively, compound **21h** could also be prepared in 63% yield via Swern oxidation of all three alcohol functions (86% per function).

b. Structural Characterization of Selected Triarylbismuthines. To further gain insight into the structure of triarylbismuthines,[21] we crystallized and analyzed by X-ray diffraction several derivatives bearing a cyclopropyl group at the *meta* position (**1f**), fluorine atoms at the 3 and 5 position (**1i**), a methoxy group at the *para* position (**1k**), an acetal at the *ortho* position (**1n**), a cyano group at the *meta* position (**1s**), a carbomethoxy function at the *para* position (**1t**), an aldehyde at the *meta* (**21b**) and *ortho* positions (**21c**), and an hydroxymethyl group at the *meta* position (**21e**).[22] The results show that the organobismuthines have a distorted trigonal pyramidal structure with Bi–C bond lengths ranging from 2.24 to 2.27 Å and C–Bi–C angles between 91° and 98° (Figure 1). These Bi–C bond lengths are consistent with known triarylbismuthines crystal structures[23] and with the 2.256 Å value estimated in the gas phase by gas electron diffraction,[24] denoting innocuous crystal packing effects. The small C–Bi–C angles are due to known relativistic effects and fall within the trend observed when going down the pnictogen family ($N > P > As > Sb > Bi$).

Interestingly, the nature and position of the substituent have little impact on the molecular structure of the organobismuthine, except in the case of the *ortho*-(diethylacetal) and *ortho*-formyl derivatives **1n** and **21c**. In these compounds with donor atoms in the *ortho* functional group, secondary intramolecular interactions are observed between the oxygen of the acetals or the carbonyls and the bismuth center (Bi···O from 3.085 to 3.255 Å in **1n** and from 2.911 to 2.991 Å in **21c**; $r_{vdW}(Bi) = 2.07$ Å, $r_{vdW}(O) = 1.52$ Å). This is not unprecedented, as bismuth is capable of acting as a weak acceptor toward other ligands or even metals[25] by accepting electrons in its C–Bi σ^* orbitals.[5a,26]

c. Palladium-Catalyzed Cross-Coupling Reaction between Organobismuthines and Aryl or Heteroaryl Halides. Multiple reports of palladium-catalyzed cross-coupling reactions involving organobismuth compounds have been disclosed in recent years.[27,28] One important aspect of triarylbismuth reagents is their ability to deliver three aryl groups per equivalent of organometallic reagent in cross-coupling reactions, making them more atom-economical than other conventional Ar–M reagents. However, in most cases, a limited array of functional groups were present on the organobismuth partner. We recently reported a palladium-catalyzed reaction to cross-couple triarylbismuthines with halogenated pyridines, pyrimidines, pyrazines, and pyridazines.[10b] Therefore, with our functionalized organobismuthines in hand, we next explored their reactivity in palladium-catalyzed

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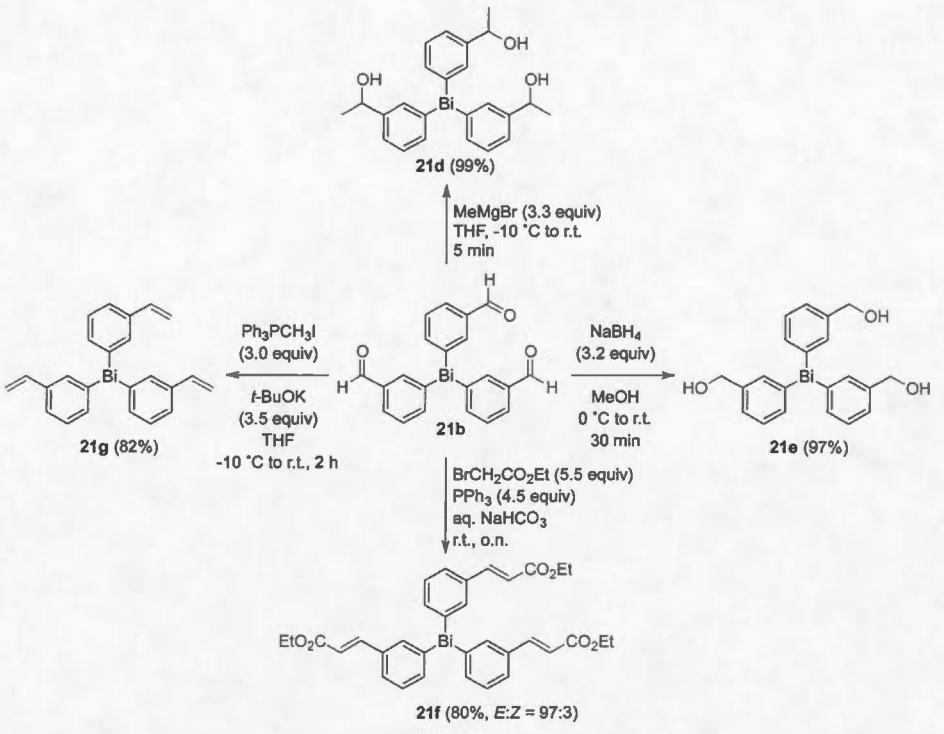
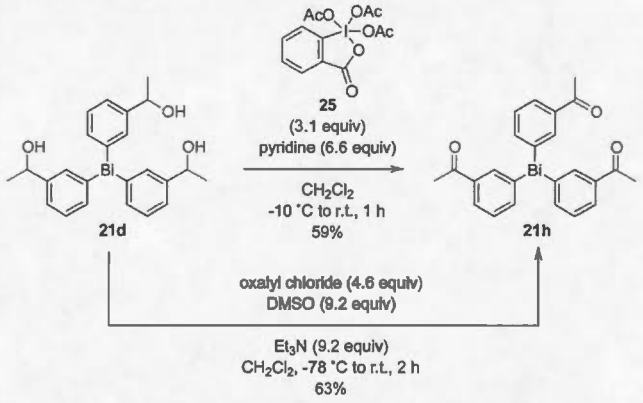
Scheme 4. Synthesis of Highly Functionalized Organobismuthines 21d–g by Derivatization of Tris(3-formylphenyl)bismuthine 21b



Scheme 5. Preparation of Ketone-Bearing Organobismuthine Derivative 21h by Dess-Martin and Swern Oxidation Starting from Tris-alcohol 21d



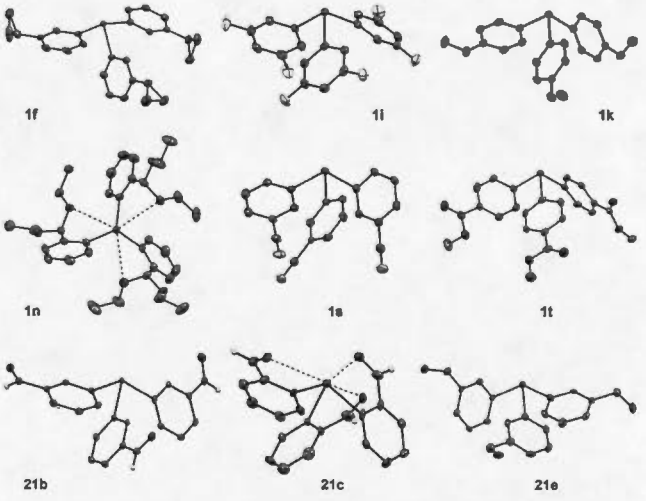


Figure 1. ORTEP view at 50% ellipsoid probability of 1f, 1i, 1k, 1n (one of three independent molecules), 1s, 1t, 21b,[10b] 21c and 21e. Hydrogen atoms are omitted for clarity, except for aldehyde functional groups. Dashed lines indicate weak intramolecular interactions between the bismuth atom and donor oxygen atoms at *ortho* positions.

cross-coupling reactions with other electrophiles in order to further probe the scope and functional group tolerance of this transformation.

First, we optimized the reaction conditions using 1.0 equiv of 4-bromobenzaldehyde **26** and 0.4 equiv of organobismuthine **21d**. Using our previously reported conditions, we obtained the desired cross-coupling product **27** in only 37% yield (Table 1, entry 1). The observed low yield shows that the coupling of highly functionalized organobismuthines represents a substantial challenge and that the reaction conditions had to be reoptimized. Suspecting that the high temperature was possibly responsible for the observed low yield, we performed the reaction at 80 °C but observed no improvement in yield (entry 2). Changing the catalyst for $PdCl_2(PPh_3)_2$ (entry 3), $Pd(OAc)_2$/S-Phos (entry 4), $Pd(OAc)_2/PPh_3$ (entry 5), or PEPPSI-*i*Pr[29] (entry 6) did not improve the yield either. Knowing the beneficial effect of lithium salts on cross-coupling reactions, as documented by Organ and others,[30] we found a substantial amelioration in yield when 2.0 equiv of lithium chloride were used as an additive (entry 7). Changing the solvent for THF (entry 8), toluene (entry 9), or a mixture of DMF and HMPA (entry 10) was detrimental to the reaction or at best inconsequential. The use of a stronger base such as potassium *tert*-butoxide led to a drastic drop in the yield of the reaction (entry 11). In addition, while potassium carbonate (entry 12) provided a similar yield as cesium carbonate (entry 7), we found that potassium phosphate (entry 13) and

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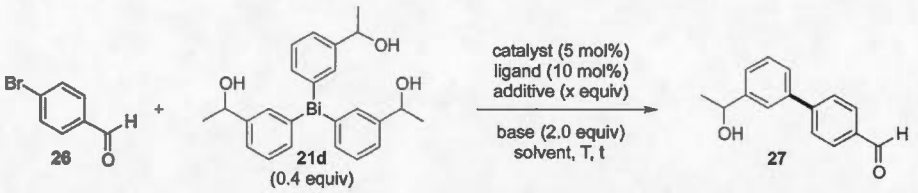
Table 1. Optimization of Reaction Conditions for the Palladium-Catalyzed Cross-Coupling Reaction of 21d with 4-Bromobenzaldehyde 26



Entry	Catalyst	Ligand	Additive (*x* equiv)	Base	Solvent	*T* (°C)	*t* (h)	Yield (%)[a]
1	$Pd(PPh_3)_4$	N.A.	N.A.	Cs_2CO_3	DMF	130	18	37
2	$Pd(PPh_3)_4$	N.A.	N.A.	Cs_2CO_3	DMF	80	6	36
3	$PdCl_2(PPh_3)_2$	N.A.	N.A.	Cs_2CO_3	DMF	80	6	31
4	$Pd(OAc)_2$	S-Phos	N.A.	Cs_2CO_3	DMF	80	6	7
5	$Pd(OAc)_2$	PPh_3	N.A.	Cs_2CO_3	DMF	80	6	31
6	PEPPSI-*i*Pr	N.A.	N.A.	Cs_2CO_3	DMF	80	6	23
7	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	Cs_2CO_3	DMF	80	6	64
8	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	Cs_2CO_3	THF	80	6	13
9	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	Cs_2CO_3	Toluene	80	6	25
10	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	Cs_2CO_3	DMF/HMPA[b]	80	6	59
11	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	*t*-BuOK	DMF	80	6	14
12	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	K_2CO_3	DMF	80	6	69
13	**$Pd(PPh_3)_4$**	**N.A.**	**LiCl (2.0 equiv)**	**K_3PO_4**	**DMF**	**80**	6	**82**
14	**$Pd(PPh_3)_4$**	**N.A.**	**LiCl (2.0 equiv)**	**Rb_2CO_3**	**DMF**	**80**	6	**75**
15	$Pd(PPh_3)_4$	N.A.	LiCl (1.0 equiv)	K_3PO_4	DMF	80	6	57
16	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	K_3PO_4[c]	DMF	80	6	48
17	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	K_3PO_4	DMF/H_2O[d]	80	6	73
18	**$Pd(PPh_3)_4$**	**N.A.**	**CuI (0.4 equiv)**	**Cs_2CO_3**	**DMF**	**80**	6	**83**

[a]Isolated yield of pure product. [b]DMF/HMPA (4:1). [c]1.0 equiv of K_3PO_4 was used. [d]DMF/H_2O (5:1).

rubidium carbonate (entry 14) were much more efficient bases in this transformation, providing the desired cross-coupling product **27** in 82% and 75% isolated yield, respectively. Lowering the number of equivalents of lithium chloride (entry 15) or potassium phosphate (entry 16) proved disadvantageous. Interestingly, the yield remained satisfactory when the reaction was run in a 5:1 ratio of DMF/H_2O, showing that strictly anhydrous conditions are not mandatory (entry 17). Rao recently reported the effect of copper salts in cross-coupling reactions involving organobismuthines.[9a] Simultaneously to Rao, we independently explored the effect of cuprous iodide as an additive and obtained a considerable improvement in the yield of the reaction (entry 18). Conditions from entries 13, 14, and 18 represent a substantial improvement over our previous protocol, as they allow the coupling reaction to be performed at a lower temperature, in a shorter time, and with a higher yield.

Having optimized the conditions for the cross-coupling of organobismuthine **21d**, we next investigated the scope of the method using organobismuthines **1a–t** and **21a–h** with selected arylhalides **28**, heteroarylhalides **29**, 2-halopyridines **2**, 2-halopyrimidines **4**, 2-halopyrazines **6**, and 3-halopyridazines **8** (Table 2). The choice of the electrophiles was motivated by the presence of functional groups that could demonstrate the applicability of our protocols in the preparation of highly functionalized compounds. In each case, our best conditions from entries 13, 14, and 18 in Table 1 (named Method A, B, and C, respectively, in Table 2) were tested in order to obtain the highest possible yield of each desired product. Thus, 4-(*N*-BOC-aminoethyl)bromobenzene **28a**, methyl 4-iodobenzoate **28b**, methyl 4-bromobenzoate **28c**, 4-bromobenzaldehyde **28d**, 2-iodo-4-furaldehyde **29a**, 6-chloropyridine-3-carboxaldehyde **2a**, 2-acetyl-6-bromopyridine **2b**, 2-chloro-4-methylpyrimidine **4a**, 2-chloro-6-dimethylaminopyrazine **6a**, and 3-chloro-6-phenylpyridazine **8a** were engaged in cross-coupling reactions with organobismuthines **1a–t** and **21a–h** to afford the corresponding products in acceptable to excellent yields. The results demonstrate that the reaction works with aryl bromides (entries 1, 3, 5), aryl or heteroaryl iodides (entries 2, 4, 6), and 2-chloro and 2-bromo nitrogenated heterocycles (entries 7–12). However, entries 2 and 3 show that iodides are slightly more reactive than bromides. The identity of the optimal set of conditions (whether A, B, or C) depended greatly on the specific combination of Ar(Het)–X and Ar_3Bi. Notwithstanding, these examples demonstrate that our protocols tolerate a wide diversity of functional groups on the electrophile and on the organobismuthine such as BOC-protected amines (**30a**), α,β-unsaturated esters (**30a**), esters (**30b,c**), ethers (**30b**), nitriles (**30c**), aldehydes (**30d**, **31a**, **3a**), dialkylamines (**7a**), and acetals (**3b**, **9b**). More striking is the ability of this method to transfer in acceptable to good yields aryl groups that possess functions that are susceptible to competitive arylation, elimination, or oxidation such as alcohols (**31a**, **7a**), ketones (**9a**), and vinyl groups (**30d**, **5a**).

d. Copper-Catalyzed *N*-Arylation of Indoles, Pyrroles, Pyrazoles, and Pyridones. We recently reported a protocol for the copper-catalyzed *N*-arylation of indoles, pyrroles, pyrazoles,[11a] and pyridones[12b] using organobismuthines with tolerance to a wide variety of functional groups. Other research groups have also reported various copper-catalyzed reactions based on trivalent or pentavalent reagents to *N*-arylate nitrogen-containing compounds.[31] To further expand the functional group diversity of our method, we tested some of the highly functionalized organobismuthines prepared in this

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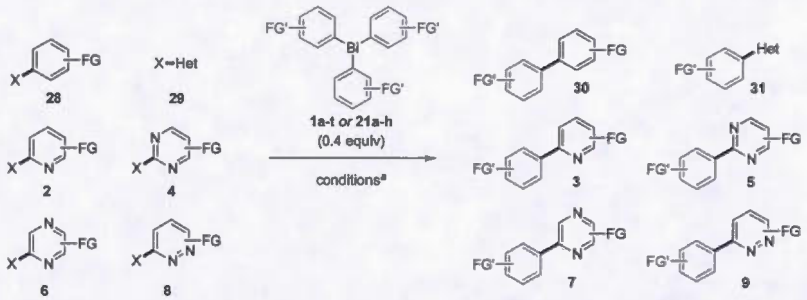
Table 2. Palladium-Catalyzed Cross-Coupling Reaction of Highly Functionalized Organobismuthines 1a–t and 21a–h with Arylhalides (28), Heteroarylhalides (29), 2-Halopyridines (2), 2-Halopyrimidines (4), 2-Halopyrazines (6), and 3-Halopyridazines (8)



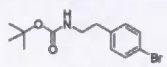
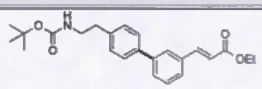
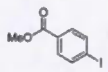
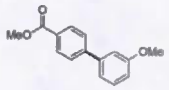
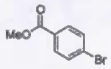
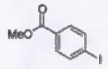
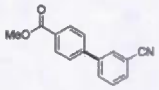
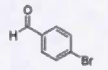
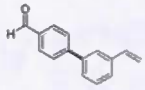
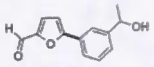
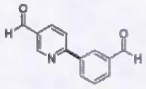
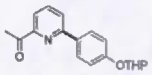
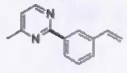
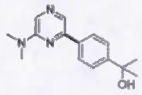
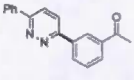
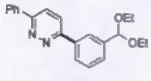
Entry	Ar(Het)–X	Ar_3Bi	Product	Yield (%)[b]
1	 28a	21f	 30a	**89 (A)** 10 (B) 80 (C)
2	 28b	1l	 30b	91 (A) 95 (B) **98 (C)**
3	 28c	1l		54 (A) **78 (B)** 66 (C)
4	 28b	1s	 30c	84 (A) **87 (B)** 41 (C)
5	 28d	21g	 30d	58 (A) 46 (B) **76 (C)**
6	 29a	21d	 31a	**82 (A)** 65 (B) 29 (C)
7	 2a	21b	 3a	36 (A) **64 (B)** 33 (C)
8	 2b	1m	 3b	0 (A) **80 (B)** 31 (C)
9	 4a	21g	 5a	**20 (A)** 12 (B) 13 (C)
10	 6a	21a	 7a	**41 (A)** 12 (B) 10 (C)
11	 8a	21h	 9a	**25 (A)** 23 (B) 12 (C)
12		1o	 9b	0 (A) **45 (B)** 0 (C)

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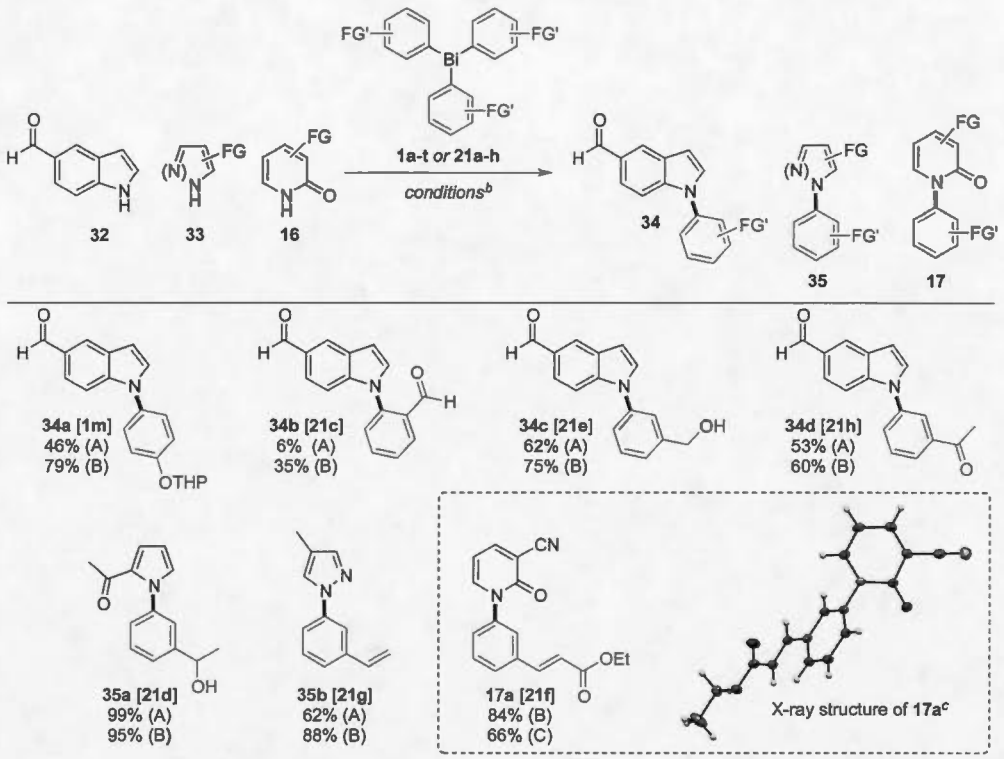
Table 2. continued

[a]Method A: Ar_3Bi (0.4 equiv), $Pd(PPh_3)_4$ (5 mol %), LiCl (2.0 equiv), K_3PO_4 (2.0 equiv), DMF, 80 °C, 6 h; Method B: Ar_3Bi (0.4 equiv), $Pd(PPh_3)_4$ (5 mol %), LiCl (2.0 equiv), Rb_2CO_3 (2.0 equiv), DMF, 80 °C, 6 h; Method C: Ar_3Bi (0.4 equiv), $Pd(PPh_3)_4$ (5 mol %), CuI (0.4 equiv), Cs_2CO_3 (2.0 equiv), DMF, 80 °C, 6 h. [b]Isolated yield of pure product.

Scheme 6. *N*-Arylation of Indole 32, Pyrrole and Pyrazole 33, and Pyridone 16 Using Highly Functionalized Organobismuthines 1a–t and 21a–h[a]



[a]The numbers in brackets indicate the organobismuthine used for the synthesis of each compound. [b]Conditions: Method A: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.1 equiv), pyridine (1.0 equiv), CH_2Cl_2, O_2, 50 °C, o.n.; Method B: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 °C, o.n.; Method C: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, air, 50 °C, o.n. [c]ORTEP diagram at 50% ellipsoid probability of compound 17a.

work in our copper-catalyzed *N*-arylation reaction. The arylations were performed at 50 °C under oxygen using 1.0 equiv of triarylbismuthine, 1.0 equiv of pyridine, and 0.1 equiv of copper acetate (Scheme 6, Method A). Every substrate was also arylated under more "forcing" conditions, that is, using stoichiometric amounts of copper acetate and 3.0 equiv of pyridine (Scheme 6, Method B). Finally, pyridones were arylated using similar conditions, except that the reactions were also performed under air (Scheme 6, Method C). As illustrated in Scheme 6, indole **32**, pyrrole and pyrazole **33**, and pyridone **16** were *N*-arylated in up to 99% yield using these conditions, demonstrating that aryl groups possessing THP-protected phenols (**34a**), aldehydes (**34b**), benzylic alcohols (**34c**), methyl ketones (**34d**), secondary alcohols (**35a**), vinyl groups (**35b**), and α,β-unsaturated esters (**17a**) can be efficiently transferred using our methods. It should be emphasized that groups that are susceptible to elimination (secondary alcohol in **35a**), oxidation (benzylic and secondary alcohols in **34c** and **35a** respectively), enolization (methyl ketone in **34d**), or arylation (alcohols in **34c** and **35a**) are also tolerated using our protocols. The main limitation of this method, as demonstrated previously,[11a] resides in the transfer of an *ortho*-substituted aryl group, as illustrated by compound **34b**.

Mukaiyama reported a copper-free method to *N*-arylate pyridones using pentavalent organobismuth reagents.[32] We demonstrated previously,[12b] based on IR analysis, that the arylation of pyridones using our copper-catalyzed reaction involving trivalent organobismuthines also leads to the *N*-arylated product (as opposed to the *O*-arylated derivative). The analysis of compound **17a** by X-ray diffraction further confirms the chemoselectivity of this arylation reaction toward nitrogen.

e. Copper-Catalyzed *O*-Arylation of Phenols. A few reports on the *O*-arylation of alcohols and phenols using organobismuth reagents have been disclosed in the literature.[33] However, most of these methods rely on pentavalent organobismuth compounds, which must be prepared from their corresponding trivalent analogues. Therefore, the development of *O*-arylation reactions directly from trivalent organobismuthines is of high interest, as it can reduce the number of steps required to obtain the desired *O*-arylated product. We recently reported an efficient and general method to prepare diarylethers via a copper-catalyzed *O*-arylation of phenols using triarylbismuthines.[12b] Using these protocols, we sought to evaluate the applicability of the highly functionalized organobismuthines in the *O*-arylation of methyl 3-hydroxybenzoate **36**. Two sets of conditions were tested: in Method A, the

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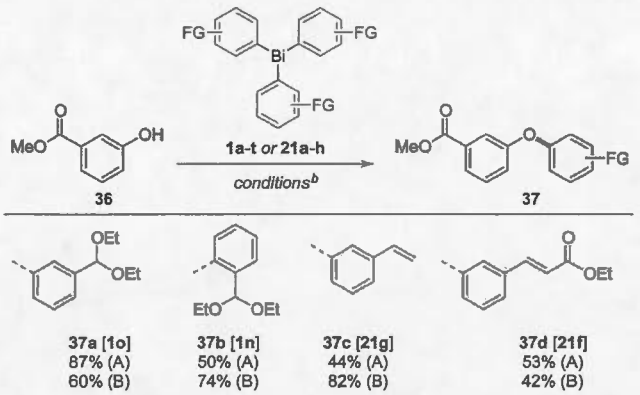
reaction was run at 50 °C for 3 h under air using 1.0 equiv of triarylbismuthine, triethylamine as the base, and a stoichiometric amount of copper acetate; in Method B, the catalyst loading was lowered to 0.3 equiv and the reaction was performed under oxygen for 16 h. As shown in Scheme 7, these

Scheme 7. *O*-Arylation of Methyl 3-Hydroxybenzoate 36 Using Highly Functionalized Organobismuthines 1a–t and 21a–h



37a [1o]	37b [1n]	37c [21g]	37d [21f]
87% (A)	50% (A)	44% (A)	53% (A)
60% (B)	74% (B)	82% (B)	42% (B)

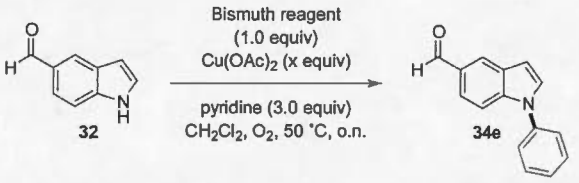
[a]The numbers in brackets indicate the organobismuthine used for the synthesis of each compound. [b]Conditions: **Method A**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 50 °C, air, 3 h; **Method B**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 50 °C, O_2, 16 h.

methods allow the transfer of aryl groups bearing a variety of groups such as acetals (37a,b), vinyl groups (37c), and α,β-unsaturated esters (37d). Contrary to the *N*-arylation of indoles, pyrroles, and pyrazoles, the *O*-arylation of phenols even shows high tolerance for substitution in the *ortho* position, as shown by compound 37b.

f. Mechanistic Investigations on the Copper-Catalyzed Arylation of Indoles and Phenols Using Trivalent and Pentavalent Organobismuth Reagents. Pentavalent organobismuth reagents have been shown to be potent arylating species in copper-catalyzed[8c,d,f,h,i] and even metal-free reactions.[8a] Barton also proposed that, in copper-catalyzed arylation reactions using triphenylbismuth, triphenylbismuth diacetate is formed *in situ* and acts as the effective arylating agent. Therefore, to compare the arylating power of trivalent and pentavalent organobismuth species, we performed the arylation on indole 32 using triphenylbismuth (Ph_3Bi, 1a) and triphenylbismuth diacetate ($Ph_3Bi(OAc)_2$, 38) in the presence and absence of copper acetate (Table 3). As expected, in the presence of copper acetate, triphenylbismuth was found to be an excellent arylating agent, providing the *N*-arylindole 34e in 97% yield (entry 1). By contrast, in the presence of copper acetate, triphenylbismuth diacetate proved to be a much less efficient arylating reagent, affording 34e in only 20% yield (entry 3). Both species were mostly inactive in the absence of copper acetate, showing that copper is essential for the *N*-arylation reaction (entries 2 and 4).

A comparative reactivity study between triphenylbismuth and triphenylbismuth diacetate was also performed on methyl 3-hydroxybenzoate 36 (Table 4). Contrary to the arylation of indoles, in the presence of copper acetate, triphenylbismuth diacetate was found to be more reactive than triphenylbismuth in the arylation of phenol 36 (entry 3 vs 1). However, similarly

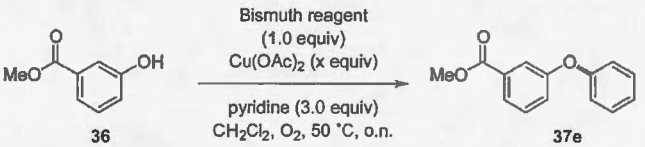
Table 3. Comparison of the Reactivity of Triphenylbismuth 1a and Triphenylbismuth Diacetate 38 in the *N*-Arylation Reaction of Indole 32



Entry	Bismuth reagent	$Cu(OAc)_2$ (*x* equiv)	Yield (%)[a]
1	Ph_3Bi (1a)	1.0	97
2	Ph_3Bi (1a)	0	2
3	$Ph_3Bi(OAc)_2$ (38)	1.0	20
4	$Ph_3Bi(OAc)_2$ (38)	0	1

[a]Yields are for isolated pure compound.

Table 4. Comparison of the Reactivity of Triphenylbismuth 1a and Triphenylbismuth Diacetate 38 in the *O*-Arylation Reaction of Phenol 36



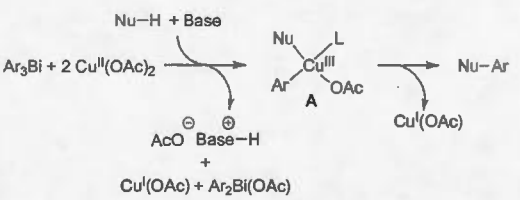
Entry	Bismuth reagent	$Cu(OAc)_2$ (*x* equiv)	Yield (%)[a]
1	Ph_3Bi (1a)	1.0	70
2	Ph_3Bi (1a)	0	0
3	$Ph_3Bi(OAc)_2$ (38)	1.0	92
4	$Ph_3Bi(OAc)_2$ (38)	0	4

[a]Yields are for isolated pure compound.

to the arylation of indole 32, in the absence of the catalyst, both reagents were unable to arylate phenol 36, showing once again that copper is essential for the *O*-arylation reaction (entries 2 and 4). The results from Table 3 and Table 4 suggest that copper acetate is necessary for both arylation reactions and that trivalent and pentavalent organobismuth species can both act as arylating agents, albeit with different efficiencies depending on the substrate.

The mechanism that we propose for the copper-catalyzed *N*- and *O*-arylation of indoles, pyrroles, pyrazoles, pyridones, and phenols (summarized by Nu–H) using triarylbismuthines involves the formation of an organocopper(III) species **A** where the deprotonated nucleophile, the aryl group, and one acetate are simultaneously ligated to the metal (Scheme 8).[34] This species would be formed by the reaction of triarylbismuthine Ar_3Bi and copper acetate, concomittantly with the

Scheme 8. Proposed Mechanism for the Copper-Catalyzed *N*- and *O*-Arylation of Indoles, Pyrroles, Pyrazoles, Pyridones, and Phenols Using Triarylbismuthines (Nu–H = Indole, Pyrrole, Pyrazole, Pyridone, or Phenol)



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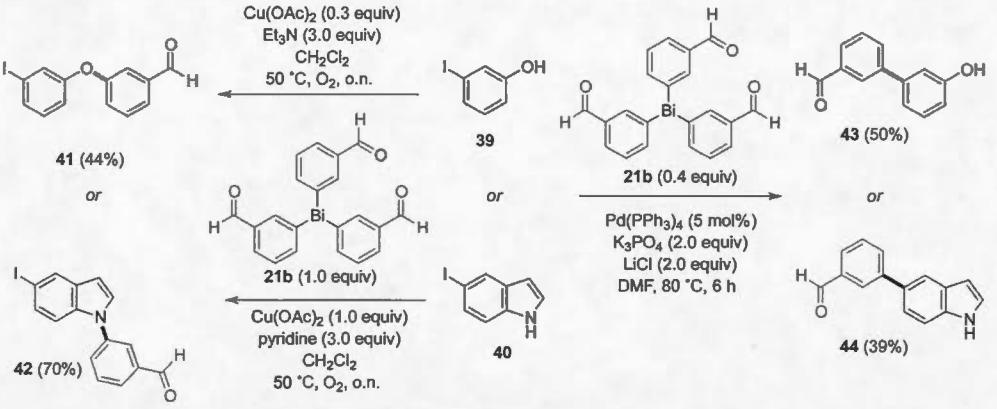
Scheme 9. Orthogonal *C*-, *N*-Arylation and *O*-Arylation of 3-Iodophenol 39 and 5-Iodoindole 40 Using Tris(3-formylphenyl)bismuthine 21b



deprotonation of the nucleophile Nu–H by the base (either triethylamine or pyridine), leading to copper(III) intermediate **A**, copper(I) acetate, and diarylbismuth acetate ($Ar_2Bi(OAc)$). Reductive elimination from species **A** would then provide the arylated nucleophile Nu–Ar. This mechanism is similar to that proposed by Barton and Finet in the copper-catalyzed arylation of amines and indoles using triphenylbismuth diacetate.[8g] Moreover, intermediate **A** was also proposed by Evans in the arylation of phenols using arylboronic acids,[35] in the Ullmann–Goldberg copper-catalyzed *N*-arylation of amines using aryl halides[36] and in detailed mechanistic studies published by Stahl on the Chan–Evans–Lam reaction.[37]

g. Orthogonal *C*-, *N*-, and *O*-Arylation Reactions on Iodo Phenols and Indoles. To further test the scope of our copper- and palladium-catalyzed methods, we explored the orthogonal transfer of aryl groups on the halogenated phenol **39** and indole **40** (Scheme 9). Using copper acetate and organobismuthine **21b**, the arylation could be directed chemoselectively to the oxygen of **39** or the nitrogen of **40**, providing **41** and **42** in 44% and 70% yield, respectively. These products would be difficult to obtain using copper(I) or palladium(0) catalysis since reaction at the aryl–I bond would compete with the desired *O*- or *N*-arylation process.[38] In addition, the palladium-catalyzed cross-coupling reaction between 3-iodophenol **39** and 5-iodoindole **40** with triarylbismuthine **21b** delivered **43** and **44**, respectively, in moderate yields. These cross-coupling reactions represent a substantial challenge since competitive dehalogenation can occur due to the presence of the phenol and N–H indole functions.

■ CONCLUSION

In summary, we demonstrated that highly functionalized triarylbismuthines can be prepared by triple functional group manipulation using acidic, nucleophilic, and reducing conditions or involving organometallic reagents or ylides. Using this approach, triarylbismuthines bearing primary, secondary, and tertiary alcohols, aldehydes, α,β-unsaturated esters, vinyl groups, and methyl ketones were prepared. These triarylbismuthines represent a class of highly functionalized and versatile organometallic reagents that are in high demand. We then developed improved protocols for the palladium-catalyzed cross-coupling reaction between these highly functionalized reagents and aryl or heteroaryl halides. These modified procedures involve lithium chloride or copper iodide as an additive and potassium phosphate or rubidium carbonate as a base and require shorter reaction times and lower temperatures. Using these protocols, highly functionalized *C*-arylated compounds were obtained in good to excellent yields. The highly functionalized organobismuthines prepared using the functional group manipulation approach were then engaged in a copper-catalyzed *N*-arylation of indoles, pyrroles, pyrazoles, and pyridones and *O*-arylation of phenols to afford highly functionalized arylated products. We then demonstrated that our palladium- and copper-catalyzed processes can be successfully used orthogonally on halogenated indoles and phenols. Preliminary mechanistic studies demonstrate that copper acetate is essential for the reaction to proceed and that the order of reactivity between the trivalent and pentavalent species depends on the nature of the substrate. Our palladium- and copper-catalyzed arylation reactions are simple to operate and show high functional group tolerance. The *C*-, *N*-, and *O*-arylation procedures developed in this work constitute an efficient and general portfolio of methods for the preparation of medicinally relevant scaffolds.

■ EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all reactions were run under argon in nonflame-dried glassware. For reactions performed under oxygen, 99.6% extra dry oxygen was used. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were prepared by conventional methods using metallic magnesium or via Knochel's procedure.[14] Anhydrous bismuth chloride >98% and triphenylbismuth diacetate 98% were purchased from Aldrich. Triarylbismuthines **1b**, **1d**, **1g**, **1l**, **1m**, **1q**, **1r**, **1s**, and **1t** were prepared according to a procedure that we previously reported.[10b] Triarylbismuthines **1c**, **1o**, and **21b** were prepared according to methods previously reported by us.[12b] Triarylbismuthines **1e**, **1f**, **1h**, **1i**, **1j**, **1k**, **1p**, **21a**, **21d**, and **21f** were prepared according to a procedure that we previously reported.[11a] Anhydrous solvents were obtained using an encapsulated solvent purification system and were further dried over 4 Å molecular sieves. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230–400 mesh silica using the indicated solvent system according to standard techniques. For compounds **1n**, **1o**, **1p**, **9b**, **37a**, and **37b**, the silica gel was washed with 3 volumes of 0.5% Et_3N/hexanes prior to performing the flash chromatography to avoid hydrolysis of the acetal. Melting points are uncorrected. Nuclear magnetic resonance spectra (^1H, ^{13}C) were recorded on a 300 or 600 MHz spectrometer. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.26

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ppm; methanol, δ 3.31 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet), coupling constant J in Hz, and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.16 ppm) or the central peak of tetradeuteromethanol (δ 49.00 ppm) as the internal standard. IR spectra were recorded on an FT-IR from thin films and are reported in reciprocal centimeters (cm^{-1}). HRMS was performed on a TOF LCMS analyzer using the electrospray (ESI) mode.

General Procedure for the Synthesis of Triarylbismuthines. In a flask equipped with a magnetic stir bar and a condenser, bismuth chloride (500 mg, 1.6 mmol) was dissolved in anhydrous THF (23 mL) under argon and was cooled to −10 °C (ice/acetone bath). The organomagnesium reagent (5.23 mmol) was slowly added dropwise under argon. The reaction mixture was stirred at room temperature for 1 h and heated at 65 °C for 30 min. After cooling to room temperature, the solution was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 × 100 mL), sat. aq. NaCl (2 × 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using the indicated solvent system to afford the desired triarylbismuthine.

*Triphenylbismuth (**1a**).* The general procedure was followed on a 2.27 mmol scale starting from bismuth chloride and phenylmagnesium bromide. The crude product was purified on silica gel (2% EtOAc/hexanes) to afford triphenylbismuth **1a** as a white solid (831 mg, 83%): mp 78−79 °C; R_f 0.33 (2% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[39] ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 6H), 7.42−7.30 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 137.7, 130.6, 127.9; IR (neat) 3133, 3053, 3011, 2582, 1943, 1871, 1810, 1566, 1471, 1422, 1053, 992, 718, 692. Anal. Calcd for $C_{18}H_{15}Bi$: C, 49.10; H, 3.43. Found: C, 49.28; H, 3.39.

*Tris(2-(diethoxymethyl)phenyl)bismuthine (**1n**).* The general procedure was followed on a 5.33 mmol scale starting from bismuth chloride and 2-(benzaldehydediethylacetal)magnesium bromide. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford tris(2-(diethoxymethyl)phenyl)bismuthine **1n** as a white solid (3.3 g, 82%): mp 78−79 °C; R_f 0.81 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 6.5, 1.4 Hz, 3H), 7.60 (dd, J = 7.3, 1.4 Hz, 3H), 7.30 (dt, J = 7.2, 1.4 Hz, 3H), 7.13 (dt, J = 7.3, 1.5 Hz, 3H), 5.53 (s, 3H), 3.55−3.34 (m, 12H), 1.01 (t, J = 7.0 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 144.5, 140.6, 131.0, 127.5, 126.8, 104.4, 61.4, 15.1; IR (neat) 3049, 2973, 2928, 2871, 1438, 1336, 1204, 1108, 1090, 1050, 757; HRMS (ESI) calcd for $[C_{33}H_{45}BiO_6 + Na]^+$: 769.2912, found 769.2868.

*Tris(2-formylphenyl)bismuthine (**21c**).* H_2O (10 mL) and HCl 12N (0.90 mL) were added at room temperature to a stirred solution of **1n** (1.0 g, 1.3 mmol) in THF (30 mL). The reaction mixture was stirred overnight and then diluted with EtOAc (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (100 mL mL), sat. aq. NaCl (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(2-formylphenyl)bismuthine **21c** as a yellow solid (213 mg, 31%): mp 179−180 °C; R_f 0.46 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 3H), 8.02 (dd, J = 7.5, 1.4 Hz, 3H), 7.59−7.54 (m, 6H), 7.34 (td, J = 7.5, 1.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 171.2, 142.3, 140.9, 136.9, 136.4, 127.7; IR (neat) 3042, 2977, 2806, 2724, 1690, 1671, 1571, 1556, 1197, 835, 759; HRMS (ESI) calcd for $[C_{21}H_{15}BiO_3 + H]^+$: 525.0898, found 525.0896.

*Tris(3-(hydroxymethyl)phenyl)bismuthine (**21e**).* A solution of tris(3-formylphenyl)bismuthine **21b** (400 mg, 0.76 mmol) in MeOH (10 mL) was cooled to 0 °C (acetone/ice bath), and $NaBH_4$ (90 mg, 2.4 mmol) was added. After 30 min, the reaction mixture was diluted with sat. aq. $NaHCO_3$ (15 mL) and extracted with EtOAc (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL) and sat. aq. NaCl (3 × 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (40% EtOAc/hexanes) to afford tris(3-(hydroxymethyl)phenyl)-bismuthine **21e** as a white solid (392 mg, 97%): mp 107−108 °C; R_f 0.39 (80% EtOAc/hexanes); ^1H NMR (300 MHz, MeOD) δ 7.77 (s, 3H), 7.63 (d, J = 6.9 Hz, 3H), 7.37−7.28 (m, 6H), 4.53 (s, 6H); ^{13}C NMR (75 MHz, MeOD) δ 156.7, 144.3, 137.6, 137.2, 131.4, 127.6, 65.3; IR (neat) 3314 (br), 3038, 2923, 2869, 1563, 1412, 1203, 1012, 776; HRMS (ESI) calcd for $[C_{21}H_{21}BiO_3 + Na]^+$: 553.1187, found 553.1177.

*Tris(3-vinylphenyl)bismuthine (**21g**).* To a solution of Ph_3PCH_3I (1.86 g, 4.58 mmol) in THF (8 mL) at −10 °C, *t*-BuOK was added (606 mg, 5.4 mmol), and the solution was stirred for 30 min. To the yellow solution, tris(3-formylphenyl)bismuthine **21b** (800 mg, 1.53 mmol) was added, and the reaction was warmed up to room temperature and stirred for 2 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL), sat. aq. NaCl (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(3-vinylphenyl)-bismuthine **21g** as a yellow oil (650 mg, 82%): R_f 0.70 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) 7.82 (s, 3H), 7.65−7.62 (m, 3H), 7.40−7.33 (m, 6H), 6.67 (dd, J = 17.6, 11.0 Hz, 3H), 5.66 (d, J = 17.6 Hz, 3H), 5.20 (d, J = 11.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 139.4, 137.2, 137.0, 135.5, 130.7, 125.7, 114.1; IR (neat) 3156, 3084, 3063, 3040, 3006, 2984, 2927, 1939, 1821, 1629, 1580, 1554, 1467, 1401, 1380, 991, 906, 791, 710. Anal. Calcd for $C_{24}H_{21}Bi$: C, 55.60; H, 4.08. Found: C, 55.87; H, 4.01.

*Tris(3-acetylphenyl)bismuthine (**21h**). Preparation via Dess-Martin oxidation*: A solution of tris(3-(1-hydroxyethyl)phenyl)bismuthine **21d** (50 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was cooled to −10 °C (acetone/ice bath), and pyridine (46 μL, 0.59 mmol) was added. After 5 min, Dess-Martin Periodinane (123 mg, 0.28 mmol) was added. After 1 h, the reaction mixture was diluted with EtOAc (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL), sat. aq. NaCl (3 × 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford tris(3-acetylphenyl)bismuthine **21h** as a white solid (30 mg, 59%). *Preparation via Swern oxidation:* A solution of oxalyl chloride (67 μL, 0.79 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was put under argon and cooled to −78 °C (acetone/ice bath). Anhydrous DMSO (112 μL, 1.57 mmol) was added dropwise to the reaction mixture and stirred for 30 min at −78 °C. Tris(3-(1-hydroxyethyl)phenyl)bismuthine **21d** (100 mg, 0.17 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and added dropwise to the reaction mixture and stirred for 1 h at −78 °C. Et_3N (219 μL, 1.57 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 × 50 mL), sat. aq. NaCl (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford tris(3-acetylphenyl)bismuthine **21h** as a white solid (61 mg, 63%): mp 85−86 °C; R_f 0.17 (20% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[40] ^1H NMR (300 MHz, $CDCl_3$) δ 8.36−8.35 (m, 3H), 7.90−7.88 (m, 6H), 7.49 (t, J = 7.5 Hz, 3H), 2.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 156.0, 142.2, 138.8, 137.1, 131.1, 128.3, 26.8; IR (neat) 3344, 3051, 3008, 2923, 1678, 1578, 1559, 1404, 1356, 1255; HRMS (ESI) calcd for $[C_{24}H_{21}BiO_3 + H]^+$: 567.1367, found 567.1400.

General Procedure for the Crystallization of Triarylbismuthines 1f, 1i, 1k, 1n, 1s, 1t, 21b, 21c, 21e and Pyridone 17a. Compounds **1f, 1i, 1k, 1n, 1s, 1t, 21b, 21c, 21e,** and **17a** were crystallized by the solvent diffusion technique according to the following procedure: 10 mg of the corresponding compound was dissolved in a minimal amount of dichloromethane in an open vial. The vial was then placed in a bigger vial filled with hexanes with a loosely tightened cap. The vials were kept at room temperature until crystals were obtained.

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General Procedures for the Palladium-Catalyzed Cross-Coupling Reactions. Compounds **3a,b**, **5a**, **7a**, **9a,b**, **27**, **30a–d**, **31a**, **43**, and **44** were prepared according to the following procedures: **Method A** (Table 1, entry 13): In a sealed tube, the aryl or heteroaryl chloride, bromide, or iodide (1.0 equiv) was dissolved in *N*,*N*-dimethylformamide (4.0 mL). Potassium phosphate (2.0 equiv) was added, followed by tetrakis(triphenylphosphine)palladium (5 mol %), lithium chloride (2.0 equiv), and triarylbismuth reagent (0.4 equiv). Argon was bubbled in the reaction mixture for 1 min. The tube was sealed and heated at 80 °C for 6 h. The reaction mixture was cooled to room temperature, diluted with sat. aq. $NaHCO_3$ (20 mL), and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 × 20 mL), sat. aq. NaCl (2 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc/hexanes as the eluent to afford the corresponding product. **Method B** (Table 1, entry 14): Same as conditions **A** except that rubidium carbonate was used instead of potassium phosphate. **Method C** (Table 1, entry 18): Same as conditions **A** except that cesium carbonate was used instead of potassium phosphate and 0.4 equiv of cuprous iodide was used instead of lithium chloride.

6-(3-Formylphenyl)nicotinaldehyde (3a). Method B was followed on a 0.095 mmol scale starting from 6-chloronicotinaldehyde **2a** and organobismuthine **21b**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **3a** as a white solid (13 mg, 64%): mp 117–118 °C; R_f 0.29 (20% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[41] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 10.12 (s, 1H), 9.15 (d, J = 1.4 Hz, 1H), 8.58 (s, 1H), 8.37 (dt, J = 7.7, 1.2 Hz, 1H), 8.26 (dd, J = 8.2, 2.1 Hz, 1H), 8.01–7.96 (m, 2H), 7.68 (t, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 190.4, 160.6, 152.4, 139.0, 137.2, 137.1, 133.3, 131.3, 130.5, 129.9, 128.9, 120.8; IR (neat) 3053, 2852, 2745, 1689, 1587, 1359, 1212, 1183, 1166, 835, 795, 740; HRMS (ESI) calcd for $[C_{13}H_9NO_2 + H]^+$: 212.0706, found 212.0708.

1-(6-(4-((Tetrahydro-2H-pyran-2-yl)oxy)phenyl)pyridine-2-yl)-ethanone (3b). Method B was followed on a 0.21 mmol scale starting from 2-acetyl-6-bromopyridine **2b** and organobismuthine **1m**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **3b** as a light pink solid (50 mg, 80%): mp 90–91 °C; R_f 0.47 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07–8.02 (m, 2H), 7.93–7.90 (m, 1H), 7.89–7.84 (m, 2H), 7.21–7.16 (m, 2H), 5.52 (t, J = 3.3 Hz, 1H), 3.97–3.89 (m, 1H), 3.67–3.60 (m, 1H), 2.82 (s, 3H), 2.10–2.00 (m, 1H), 1.93–1.89 (m, 2H), 1.88–1.60 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 158.5, 156.4, 153.4, 137.6, 132.0, 128.3, 122.9, 119.3, 116.8, 96.4, 62.2, 30.4, 25.9, 25.3, 18.8; IR (neat) 3060, 2943, 2872, 2840, 1696, 1606, 1513, 1449, 1355, 1239, 1177, 1036, 960, 919, 845, 806, 739, 613, 593; HRMS (ESI): calcd for $[C_{18}H_{19}NO_3 + H]^+$: 298.1438, found 298.1426.

4-Methyl-2-(3-vinylphenyl)pyrimidine (5a). Method A was followed on a 0.40 mmol scale starting from 2-chloro-4-methylpyrimidine **4a** and organobismuthine **21g**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **5a** as a yellow oil (16 mg, 20%): R_f 0.60 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 5.1 Hz, 1H), 8.48 (t, J = 1.9 Hz, 1H), 8.34 (dt, J = 7.7, 1.5 Hz, 1H), 7.54 (dt, J = 7.7, 1.6 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.05 (d, J = 5.0 Hz, 1H), 6.82 (dd, J = 17.6, 10.9 Hz, 1H), 5.87 (dd, J = 17.4, 0.9 Hz, 1H), 5.30 (dd, J = 10.8, 0.9 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 164.3, 156.9, 138.2, 138.0, 136.8, 128.9, 128.3, 127.8, 126.3, 118.8, 114.4, 24.6; IR (neat) 3061, 3038, 2954, 2928, 2867, 1692, 1572, 1555, 1431, 1384, 1364, 912, 789; HRMS (ESI) calcd for $[C_{13}H_{12}N_2 + H]^+$: 197.1073, found 197.1080.

2-(4-(6-(Dimethylamino)pyrazin-2-yl)phenyl)propan-2-ol (7a). Method A was followed on a 0.32 mmol scale starting from 6-chloro-*N*,*N*-dimethylpyrazin-2-amine **6a** and organobismuthine **21a**. The crude material was purified on silica gel (40% EtOAc/hexanes) to afford **7a** as a yellow solid (34 mg, 41%): mp 158–159 °C; R_f 0.20 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.99–7.94 (m, 2H), 7.91 (s, 1H), 7.60–7.56 (m, 2H), 3.17 (s, 6H), 2.37 (s(br), 1H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 150.5, 149.2, 136.0, 128.4, 127.9, 126.8, 125.0, 72.6, 37.6, 31.9; IR (neat) 3371 (br), 3059, 2971, 2923, 2869, 1583, 1566, 1527, 1425, 1402, 1372, 1186, 1151, 996, 831; HRMS (ESI) calcd for $[C_{15}H_{19}N_3O + H]^+$: 258.1601, found 258.1603.

1-(3-(6-Phenylpyridazin-3-yl)phenyl)ethanone (9a). Method A was followed on a 0.26 mmol scale starting from 3-chloro-6-phenylpyridazine **8a** and organobismuthine **21h**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **9a** as a yellow solid (18 mg, 25%): mp 130–131 °C; R_f 0.25 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (t, J = 1.9 Hz, 1H), 8.41 (dt, J = 7.9, 1.4 Hz, 1H), 8.18 (dd, J = 8.1, 1.9 Hz, 2H), 8.11 (dt, J = 6.5, 1.5 Hz, 1H), 8.05–7.97 (m, 2H), 7.67 (t, J = 7.8 Hz, 1H), 7.60–7.52 (m, 3H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 158.1, 156.8, 137.9, 136.7, 135.9, 131.4, 130.4, 129.8, 129.5, 129.2, 127.1, 126.9, 124.5, 124.4, 27.0; IR (neat) 3061, 3000, 2932, 1683, 1601, 1585, 1432, 1398, 1358, 1236, 689; HRMS (ESI) calcd for $[C_{18}H_{14}N_2O + H]^+$: 275.1179, found 275.1191.

3-(3-(Diethoxymethyl)phenyl)-6-phenylpyridazine (9b). Method B was followed on a 0.10 mmol scale starting from 3-chloro-6-phenylpyridazine **8a** and organobismuthine **1o**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **9b** as a beige solid (15 mg, 45%): mp 88–89 °C; R_f 0.36 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (t, J = 1.8 Hz, 1H), 8.19–8.14 (m, 3H), 7.95 (dd, J = 11.3, 9.0 Hz, 2H), 7.63 (dt, J = 7.7, 1.5 Hz, 1H), 7.58–7.51 (m, 4H), 5.61 (s, 1H), 3.73–3.54 (m, 4H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 157.7, 140.3, 136.3, 130.2, 129.2, 129.1, 128.5, 127.1, 125.4, 124.5, 124.3, 101.5, 61.4, 15.4; IR (neat) 3052, 2974, 2917, 2848, 1704, 1450, 1397, 1328, 1095, 1050, 997, 780, 690; HRMS (ESI): calcd for $[C_{21}H_{22}N_2O_2 + H]^+$: 335.1754, found 335.1767.

3′-(1-Hydroxyethyl)-[1,1′-biphenyl]-4-carbaldehyde (27). Method C was followed on a 0.27 mmol scale starting from 4-bromobenzaldehyde **26** and organobismuthine **21d**. The crude material was purified on silica gel (25% EtOAc/hexanes) to afford **27** as a yellow oil (51 mg, 83%): R_f 0.22 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.97–7.93 (m, 2H), 7.78–7.74 (m, 2H), 7.67–7.66 (m, 1H), 7.55 (td, J = 7.1, 1.9 Hz, 1H), 7.49–7.41 (m, 2H) 4.99 (q, J = 6.5 Hz, 1H), 1.82 (s(br), 1H), 1.56 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 147.2, 146.8, 139.9, 135.3, 130.3, 129.2, 127.8, 126.5, 125.6, 124.5, 70.3, 25.4; IR (neat) 3422 (br), 3059, 3032, 2971, 2923, 2836, 2731, 1689, 1603, 1567, 1170, 1077, 794, 703; HRMS (ESI) calcd for $[C_{15}H_{14}O_2 + H]^+$: 227.1067, found 227.1068.

(E)-Ethyl 3-(4′-(2-((tert-Butoxycarbonyl)amino)ethyl)-[1,1′-biphenyl]-3-yl)acrylate (30a). Method A was followed on a 0.17 mmol scale starting from *tert*-butyl 4-bromophenethylcarbamate **28a** and organobismuthine **21f**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **30a** as a yellow solid (60 mg, 89%): mp 111–112 °C; R_f 0.52 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 16.0 Hz, 1H), 7.73 (s, 1H), 7.61–7.59 (m, 1H), 7.55–7.53 (m, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.45–7.40 (m, 2H), 7.06 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 16.0 Hz, 1H), 4.53 (s(br), 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.34 (q, J = 6.4 Hz, 2H), 2.75 (t, J = 6.9 Hz, 2H), 1.43 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 155.9, 144.3, 141.3, 138.1, 135.2, 131.7, 130.6, 129.6, 129.0, 127.3, 126.9, 120.3, 119.0, 79.4, 60.7, 41.7, 35.8, 28.5, 14.4; IR (neat) 3437, 3363, 2977, 2931, 2866, 1703, 1637, 1508, 1488, 1365, 1307, 1267, 1248, 1163, 1036, 1011, 789. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72,89; H, 7.39; N, 3.54. Found: C, 72.90; H, 7.41; N, 3.52.

Methyl 3′-Methoxy-[1,1′-biphenyl]-4-carboxylate (30b). Starting from methyl 4-iodobenzoate 28b: Method C was followed on a 0.19 mmol scale starting from methyl 4-iodobenzoate **28b** and organobismuthine **1l**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **30b** as a white solid (45 mg, 98%). *Starting from methyl 4-bromobenzoate 28c:* Method B was followed on a 0.30 mmol scale starting from methyl 4-bromobenzoate **28c** and organobismuthine **1l**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **30b** as a white solid (57 mg, 78%): mp 55–56 °C; R_f 0.50 (10% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[42] ^{1}H NMR (600 MHz, $CDCl_3$) δ

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8.10 (d, J = 4.2 Hz, 2H), 7.65 (d, J = 4.2 Hz, 2H), 7.38 (t, J = 3.9 Hz, 1H), 7.20 (d, J = 3.8 Hz, 1H), 7.16–7.15 (m, 1H), 6.94 (dd, J = 4.1, 1.0 Hz, 1H) 3.94 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 160.1, 145.6, 141.6, 130.2, 130.1, 129.1, 127.2, 119.9, 113.6, 113.1, 55.5, 52.2; IR (neat) 3064, 2999, 2950, 2835, 1932, 1716, 1605, 1434, 1270, 1103, 1017, 849, 764, 694; HRMS (ESI): calcd for $[C_{15}H_{14}O_3 + H]^+$: 243.1016, found 243.1016.

Methyl 3′-Cyano-[1,1′-biphenyl]-4-carboxylate (30c). Method B was followed on a 0.30 mmol scale starting from methyl 4-iodobenzoate **28b** and organobismuthine **1s**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **30c** as a white solid (62 mg, 87%): mp 137–138 °C; R_f 0.60 (20% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14–8.10 (m, 2H), 7.88–7.87 (m, 1H), 7.85–7.81 (m, 1H), 7.68–7.54 (m, 4H) 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 143.2, 141.3, 131.7, 131.6, 130.9, 130.5, 130.1, 129.9, 127.2, 118.6, 113.3, 52.4; IR (neat) 3411, 3068, 2954, 2836, 2232, 1608, 1429, 1281, 1186, 1102, 764, 684; HRMS (ESI): calcd for $[C_{15}H_{11}NO_2 + H]^+$: 238.0863, found 238.0870.

3′-Vinyl-[1,1′-biphenyl]-4-carbaldehyde (30d). Method C was followed on a 0.17 mmol scale starting from 4-bromobenzaldehyde **28d** and organobismuthine **21g**. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **30d** as a colorless oil (27 mg, 76%): R_f 0.30 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.98–7.94 (m, 2H), 7.79–7.74 (m, 2H), 7.66–7.65 (m, 1H), 7.55–7.51 (m, 1H), 7.49–7.42 (m, 2H), 6.80 (dd, J = 17.6, 10.8 Hz, 1H), 5.84 (d, J = 17.6 Hz, 1H), 5.33 (d, J = 10.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 147.2, 140.2, 138.5, 136.6, 135.4, 130.4, 129.3, 127.9, 126.9, 126.3, 125.5, 114.9; IR (neat) 3407 (br), 3057, 2916, 2844, 2734, 1692, 1601, 1384, 1209, 1167, 988, 836, 791, 699; HRMS (ESI): calcd for $[C_{15}H_{12}O + H]^+$: 209.0961, found 209.0965.

5-(3-(1-Hydroxyethyl)phenyl)furan-2-carbaldehyde (31a). Method A was followed on a 0.23 mmol scale starting from 5-iodofuran-2-carbaldehyde **29a** and organobismuthine **21d**. The crude material was purified on silica gel (30% EtOAc/hexanes) to afford **31a** as a yellow oil (41 mg, 82%): R_f 0.25 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.85 (s, 1H), 7.74–7.71 (m, 1H), 7.43–7.41 (m, 2H), 7.32 (d, J = 3.7 Hz, 1H), 6.86 (d, J = 3.7 Hz, 1H), 4.97 (q, J = 6.5 Hz, 1H), 1.96 (s(br), 1H), 1.53 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 159.5, 151.9, 146.9, 129.2, 129.1, 126.8, 124.4, 123.8, 122.3, 107.9, 70.1, 25.4; IR (neat) 3416 (br), 3103, 2972, 2916, 2871, 2821, 1663, 1516, 1468, 1426, 1265, 1071, 1028, 792; HRMS (ESI) calcd for $[C_{13}H_{12}O_3 + H]^+$: 217.0859, found 217.0867.

3′-Hydroxy-[1,1′-biphenyl]-3-carbaldehyde (43). Method A was followed on a 0.23 mmol scale starting from 3-iodophenol **39** and organobismuthine **21b**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **43** as a white solid (23 mg, 50%): mp 88–89 °C; R_f 0.38 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.08 (t, J = 1.6 Hz, 1H), 7.86 (dt, J = 7.4, 1.4 Hz, 2H), 7.61 (t, J = 7.7 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.20 (dt, J = 7.6, 1.4 Hz, 1H), 7.11 (t, J = 2.2 Hz, 1H), 6.87 (ddd, J = 8.1, 2.5, 0.8 Hz, 1H), 4.97 (s(br), 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 156.3, 141.9, 141.5, 137.0, 133.3, 130.4, 129.7, 129.1, 128.3, 119.8, 115.2, 114.3; IR (neat) 3363 (br), 3062, 2927, 2831, 2734, 1686, 1599, 1588, 1458, 1308, 1212, 1169, 779, 690; HRMS (ESI) calcd for $[C_{13}H_{10}O_2 + H]^+$: 199.0754, found 199.0750.

3-(1H-Indol-5-yl)benzaldehyde (44). Method A was followed on 0.21 mmol scale starting from 5-iodo-*1H*-indole **40** and organobismuthine **21b**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **44** as a yellow oil (18 mg, 39%): R_f 0.43 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.26 (s(br), 1H), 8.17 (t, J = 1.8 Hz, 1H), 7.95–7.91 (m, 1H), 7.91 (s, 1H), 7.82 (dt, J = 7.6, 1.4 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (s, 2H), 7.28 (t, J = 2.9 Hz, 1H), 6.64 (dd, J = 3.1, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 143.6, 137.0, 135.8, 133.4, 132.0, 129.5, 128.6, 127.8, 125.3, 121.8, 119.6, 111.6, 103.1; IR (neat) 3414 (br), 3057, 2825, 2738, 1689, 1599, 1578, 1466, 1424, 1316, 1197, 792; HRMS (ESI) calcd for $[C_{15}H_{11}NO + H]^+$: 222.0913, found 222.0924.

General Procedure for the *N*-Arylation of Indoles, Pyrroles, Pyrazoles, and Pyridones. Compounds **17a**, **34a–e**, **35a,b**, and **42** were prepared according to the following procedures: **Method A:** In a sealed tube, the triarylbismuthine (1.0 equiv) was added, followed by copper(II) acetate (0.1 equiv) and the indole, pyrrole, pyrazole, or pyridone (1.0 equiv). The reagents were dissolved in anhydrous dichloromethane (4 mL), and pyridine (1.0 equiv) was added to the mixture. The reaction tube was purged with dry oxygen for 30 s, sealed, and heated at 50 °C overnight. The reaction mixture was cooled to room temperature, transferred, and rinsed with EtOAc in a round-bottom flask. Silica gel was added, and the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using the indicated solvent system as the eluent to give the corresponding product. **Method B:** Same as method **A** except for copper(II) acetate (1.0 equiv instead of 0.1 equiv) and pyridine (3.0 equiv instead of 1.0 equiv). **Method C:** Same as method **A** except that 1.0 equiv of copper(II) acetate and 3.0 equiv of pyridine were used and the reaction was performed at 50 °C under air in a sealed tube overnight.

(E)-Ethyl 3-(3-(3-Cyano-2-oxopyridin-1(2H)-yl)phenyl)acrylate (17a). Method B was followed on a 0.21 mmol scale starting from 2-oxo-1,2-dihydropyridine-3-carbonitrile and organobismuthine **21f**. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **17a** as a white solid (52 mg, 84%): mp 173–174 °C; R_f 0.37 (60% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.1, 2.1 Hz, 1H), 7.66 (d, J = 16.1 Hz, 1H), 7.63–7.59 (m, 2H), 7.54 (d, J = 7.7 Hz, 1H), 7.52–7.51 (m, 1H), 7.38 (dt, J = 7.9, 1.6 Hz, 1H), 6.45 (d, J = 16.1 Hz, 1H), 6.38 (t, J = 7.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.3, 148.0, 142.9, 142.6, 140.1, 136.4, 130.3, 129.0, 127.7, 125.6, 120.5, 115.3, 107.0, 105.8, 60.9, 14.4; IR (neat) 3080, 2977, 2924, 2905, 2228, 1707, 1662, 1640, 1542, 1269, 1181; HRMS (ESI) calcd for $[C_{17}H_{14}N_2O_3 + H]^+$: 295.1077, found 295.1099.

1-(4-((Tetrahydro-2H-pyran-2-yl)oxy)phenyl)-1H-indole-5-carbaldehyde (34a). Method B was followed on a 0.17 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **1m**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **34a** as a yellow solid (43 mg, 79%): mp 105–106 °C; R_f 0.52 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.20 (s, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.53–7.46 (m, 1H), 7.41–7.30 (m, 3H), 7.26–7.20 (m, 2H), 6.80 (d, J = 3.2 Hz, 1H), 5.49 (t, J = 3.3 Hz, 1H), 3.99–3.91 (m, 1H), 3.70–3.63 (m, 1H), 2.08–1.99 (m, 1H), 1.94–1.89 (m, 2H), 1.78–1.62 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 156.5, 139.7, 132.7, 130.5, 130.0, 128.8, 126.5, 126.2, 122.6, 117.6, 111.2, 104.8, 96.7, 62.3, 30.4, 25.3, 18.8; IR (neat) 3101, 3039, 2943, 2873, 2850, 2715, 1683, 1615, 1509, 1330, 1237, 1221, 1201, 1102, 1044, 921, 731; HRMS (ESI) calcd for $[C_{20}H_{19}NO_3 + H]^+$: 322.1438, found 322.1430.

1-(2-Formylphenyl)-1H-indole-5-carbaldehyde (34b). Method B was followed on a 0.17 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **21c**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **34b** as a yellow oil (15 mg, 35%): R_f 0.44 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.63 (s, 1H), 8.25 (d, J = 0.9 Hz, 1H), 8.13 (dd, J = 7.7, 1.5 Hz, 1H), 7.83–7.77 (m, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.51 (dd, J = 7.9, 0.8 Hz, 1H), 7.39 (d, J = 3.3 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 6.91 (dd, J = 3.3, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 189.1, 141.5, 141.0, 135.4, 132.3, 131.9, 131.7, 130.7, 129.2, 128.7, 128.4, 126.4, 123.6, 110.9, 106.0; IR (neat) 3357, 3106, 3065, 2977, 2920, 2867, 2745, 1687, 1597, 1490, 1331, 1195; HRMS (ESI) calcd for $[C_{16}H_{11}NO_2 + H]^+$: 250.0868, found 250.0873.

1-(3-(Hydroxymethyl)phenyl)-1H-indole-5-carbaldehyde (34c). Method B was followed on a 0.09 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **21e**. The crude product was purified on silica gel (30% EtOAc/hexanes) to afford **34c** as a yellow oil (17 mg, 75%): R_f 0.15 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.22 (d, J = 1.1 Hz, 1H), 7.78 (dd, J = 8.7, 1.5 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.55–7.53 (m, 2H), 7.44–7.41 (m, 3H), 6.84 (d, J = 3.3 Hz, 1H), 4.83 (d, J = 4.0 Hz, 2H), 1.84 (t, J = 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 143.2,

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139.3, 130.2, 130.1, 130.0, 129.2, 126.5, 125.8, 123.8, 123.1, 122.8, 111.2, 105.4, 105.4, 64.8; IR (neat) 3411 (br), 3105, 3055, 2920, 2858, 2815, 2727, 1682, 1601, 1589, 1565, 1493, 1449, 1331, 1223, 1103, 1032, 894, 726, 698; HRMS (ESI) calcd for $[C_{16}H_{13}NO_2 + H]^+$: 252.1019, found 252.1012.

1-(3-Acetylphenyl)-1H-indole-5-carbaldehyde (34d). Method B was followed on a 0.17 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **21h**. The crude product was purified on silica gel (30% EtOAc/hexanes) to afford **34d** as a yellow oil (27 mg, 60%): R_f 0.34 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.23 (d, J = 1.5 Hz, 1H), 8.09 (t, J = 1.8 Hz, 1H), 8.00 (dt, J = 7.4, 1.6 Hz, 1H), 7.81 (dd, J = 8.7, 1.6 Hz, 1H), 7.73 (dt, J = 8.0, 1.7 Hz, 1H), 7.70–7.65 (m, 1H), 7.57 (d, J = 8.7 Hz, 1H) 7.45 (d, J = 3.3 Hz, 1H), 6.87 (d, J = 3.3 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 192.3, 139.6, 139.2, 139.0, 130.5, 130.4, 129.9, 129.3, 129.1, 127.3, 126.5, 124.3, 123.2, 111.0, 106.0, 26.9; IR (neat) 3357, 3103, 3057, 2924, 2825, 2741, 1682, 1599, 1586, 1491, 1445, 1330, 1236, 1105, 769; HRMS (ESI) calcd for $[C_{17}H_{13}NO_2 + H]^+$: 264.1019, found 264.1012.

1-Phenyl-1H-indole-5-carbaldehyde (34e). Method B was followed on a 0.29 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **1a**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **34e** as a yellow oil (62 mg, 97%): R_f 0.14 (10% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[44] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.22 (s, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.61–7.54 (m, 3H), 7.52–7.49 (m, 2H), 7.46–7.41 (m, 2H), 6.84 (d, J = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 139.4, 139.1, 130.3, 130.2, 130.0, 129.2, 127.6, 126.5, 124.9, 122.8, 111.2, 105.4; IR (neat) 3060, 2962, 2921, 2815, 2778, 2709, 1683, 1593, 1498, 1448, 1338, 1222, 1103, 886, 755, 695; HRMS (ESI): calcd for $[C_{15}H_{11}NO + H]^+$: 222.0913, found 222.0919.

1-(1-(3-(1-Hydroxyethyl)phenyl)-1H-pyrrol-2-yl)ethanone (35a). Method A was followed on a 0.13 mmol scale starting from 1-(1*H*-pyrrol-2-yl)ethanone and organobismuthine **21d**. The crude product was purified on silica gel (35% EtOAc/hexanes) to afford **35a** as a yellow oil (30 mg, 99%): R_f 0.19 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.32 (m, 2H), 7.26 (s, 1H), 7.13–7.08 (m, 2H), 6.94 (dd, J = 2.4, 1.8 Hz, 1H), 6.28 (dd, J = 4.1, 2.6 Hz, 1H), 4.84 (q, J = 6.4 Hz, 1H), 3.51 (s(br), 1H), 2.38 (s, 3H), 1.45 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 147.1, 140.8, 131.5, 131.4, 128.6, 124.8, 124.7, 123.4, 120.9, 109.3, 69.6, 27.2, 25.0; IR (neat) 3409 (br), 3114, 3057, 2973, 2920, 2867, 1644, 1489, 1405, 1366, 1348, 1110, 1084, 1050, 940, 793, 738, 654; HRMS (ESI) calcd for $[C_{14}H_{15}NO_2 + H]^+$: 230.1176, found 230.1178.

4-Methyl-1-(3-vinylphenyl)-1H-pyrazole (35b). Method B was followed on a 0.43 mmol scale starting from 4-methyl-1*H*-pyrazole and organobismuthine **21g**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **35b** as a yellow oil (70 mg, 88%): R_f 0.53 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (t, J = 2.0 Hz, 1H), 7.70–7.69 (m, 1H), 7.53 (s, 1H), 7.51–7.48 (m, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.27 (dt, J = 7.7, 1.5 Hz, 1H), 6.73 (dd, J = 17.6, 10.8 Hz, 1H), 5.82 (d, J = 17.6 Hz, 1H), 5.31 (d, J = 10.9 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 140.6, 139.1, 136.3, 129.6, 125.5, 123.9, 118.4, 118.0, 116.6, 115.1, 9.1; IR (neat) 3141, 3118, 3065, 2926, 2863, 1695, 1606, 1585, 1533, 1489, 1454, 1399, 1362, 1047, 791, 755, 697; HRMS (ESI) calcd for $[C_{12}H_{12}N_2 + H]^+$: 185.1073, found 185.1078.

3-(5-Iodo-1H-indol-1-yl)benzaldehyde (42). Method B was followed on 0.12 mmol scale starting from 5-iodo-1*H*-indole **40** and organobismuthine **21b**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **42** as a yellow oil (29 mg, 70%): R_f 0.54 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.03 (d, J = 1.5 Hz, 1H), 7.98–7.97 (m, 1H), 7.87 (dt, J = 7.0, 1.6 Hz, 1H), 7.76–7.68 (m, 2H), 7.49 (dd, J = 8.7, 1.6 Hz, 1H), 7.33 (s, 1H), 7.31 (d, J = 5.2 Hz, 1H), 6.65 (d, J = 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 140.3, 138.0, 134.9, 132.1, 131.2, 130.7, 130.3, 129.9, 128.5, 128.4, 124.3, 112.3, 103.8, 84.4; IR (neat) 3106, 3068, 2958, 2920, 2829, 2734, 1698, 1588, 1513, 1487, 1459, 1237, 793; HRMS (ESI) calcd for $[C_{15}H_{10}INO + H]^+$: 347.9880, found 347.9896.

General Procedure for the *O*-Arylation of Phenols. Compounds **37a–e** and **41** were prepared according to the following procedures: **Method A:** In a sealed tube, the phenol (1.0 equiv) was dissolved in nonanhydrous solvent grade dichloromethane (3 mL). The organobismuthine (1.0 equiv) was added followed by copper(II) acetate (1.0 equiv) and Et_3N (3.0 equiv). The tube was sealed and heated at 50 °C for 3 h under air. The reaction mixture was cooled to room temperature, and silica gel was added. The mixture was concentrated under reduced pressure, and the crude product was purified by flash column chromatography using the indicated solvent system to afford the corresponding product. **Method B:** Same as method **A** except that 0.3 equiv of $Cu(OAc)_2$ was used and the reaction was performed under O_2 for 16 h.

Methyl 3-(3-(Diethoxymethyl)phenoxy)benzoate (37a). Method A was followed on a 0.26 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **1o**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **37a** as a colorless oil (75 mg, 87%): R_f 0.62 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dt, J = 7.7, 1.3 Hz, 1H), 7.65 (dd, J = 2.6, 1.5 Hz, 1H), 7.42–7.31 (m, 2H), 7.27–7.24 (m, 1H), 7.20 (ddd, J = 8.2, 2.6, 1.1 Hz, 1H), 7.16 (t, J = 2.1 Hz, 1H), 6.97 (ddd, J = 7.9, 2.6, 1.2 Hz, 1H), 5.48 (s, 1H), 3.88 (s, 3H), 3.67–3.48 (m, 4H), 1.22 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 157.5, 156.8, 141.6, 132.0, 129.9, 129.8, 124.4, 123.4, 122.2, 119.6, 119.0, 117.6, 101.1, 61.2, 52.4, 15.3; IR (neat) 3068, 2973, 2920, 2878, 1726, 1684, 1582, 1483, 1441, 1357, 1270, 1049, 901, 794, 753, 696; HRMS (ESI) calcd for $[C_{19}H_{22}O_5 + Na]^+$: 353.1359, found 353.1369.

Methyl 3-(2-(Diethoxymethyl)phenoxy)benzoate (37b). Method B was followed on a 0.16 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **1n**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **37b** as a colorless oil (39 mg, 74%): R_f 0.73 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.73 (m, 1H), 7.70 (dd, J = 7.6, 1.8 Hz, 1H), 7.64 (dd, J = 2.6, 1.5 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.28 (dt, J = 7.4, 1.8 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.14 (ddd, J = 8.3, 2.6, 1.1 Hz, 1H), 6.88 (dd, J = 8.2, 1.5 Hz, 1H), 5.73 (s, 1H), 3.89 (s, 3H), 3.70–3.60 (m, 2H), 3.56–3.49 (m, 2H), 1.16 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 158.2, 153.8, 131.9, 131.2, 129.9, 129.7, 128.0, 124.4, 124.0, 122.6, 119.7, 119.0, 97.6, 62.4, 52.3, 15.2; IR (neat) 3066, 2975, 2877, 1724, 1580, 1482, 1444, 1271, 1230, 1202, 1052, 994, 905, 754; HRMS (ESI) calcd for $[C_{19}H_{22}O_5 + Na]^+$: 353.1359, found 353.1363.

Methyl 3-(3-Vinylphenoxy)benzoate (37c). Method B was followed on a 0.13 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **21g**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **37c** as a yellow oil (27 mg, 82%): R_f 0.74 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dt, J = 7.7, 1.3 Hz, 1H), 7.66 (dd, J = 2.6, 1.6 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.23–7.17 (m, 2H), 7.07 (t, J = 2.0 Hz, 1H), 6.90 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 6.67 (dd, J = 17.6, 10.9 Hz, 1H), 5.70 (dd, J = 17.6, 0.8 Hz, 1H), 5.27 (d, J = 10.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 157.5, 157.1, 139.8, 136.3, 132.1, 130.1, 129.9, 124.5, 123.4, 122.0, 119.7, 118.6, 116.8, 115.0, 52.4; IR (neat) 3076, 3008, 2952, 2928, 2844, 1724, 1573, 1485, 1442, 1275, 1250, 1208, 1143, 1098, 991; HRMS (ESI) calcd for $[C_{16}H_{14}O_3 + H]^+$: 255.1016, found 255.1020.

(E)-Methyl 3-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenoxy)-benzoate (37d). Method A was followed on a 0.25 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **21f**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **37d** as a yellow oil (43 mg, 53%): R_f 0.61 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (td, J = 7.8, 1.3 Hz, 1H), 7.67–7.66 (m, 1H), 7.62 (d, J = 16.0 Hz, 1H), 7.46–7.40 (m, 1H), 7.39–7.34 (m, 1H), 7.30–7.27 (m, 1H), 7.22 (ddd, J = 8.2, 2.6, 1.1 Hz, 1H), 7.14 (t, J = 2.1 Hz, 1H), 7.02 (ddd, J = 8.0, 1.9, 1.2 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 166.5, 157.5, 157.0, 143.8, 136.6, 132.2, 130.5, 130.1, 124.9, 123.7, 123.6, 120.7, 120.0, 119.3, 118.0, 60.7, 52.4, 14.4; IR (neat) 3065,

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2980, 2953, 2901, 1709, 1639, 1575, 1484, 1442, 1269, 1230, 1177, 1097, 1036, 983, 756; HRMS (ESI) calcd for $[C_{19}H_{18}O_5 + H]^+$: 327.1227, found 327.1224.

Methyl 3-Phenoxybenzoate (37e). A modified method B using 1.0 equiv of $Cu(OAc)_2$ instead of 0.3 equiv and pyridine instead of triethylamine was followed on a 0.33 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **1a**. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford 37e as a pale yellow oil (53 mg, 70%): R_f 0.43 (10% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[45] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (td, J = 7.7, 1.3 Hz, 1H), 7.68 (t, J = 2.1 Hz, 1H), 7.43–7.32 (m, 3H), 7.21 (dd, J = 8.2, 2.5 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 8.2 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 157.5, 156.7, 131.9, 129.9, 129.8, 124.3, 123.8, 123.3, 119.6, 119.1, 52.2; IR (neat) 3068, 2947, 2840, 1722, 1582, 1479, 1437, 1266, 1228, 1091, 988, 904, 749, 688; HRMS (ESI): calcd for $[C_{14}H_{12}O_3 + H]^+$: 229.0859, found 229.0863.

3-(3-Iodophenoxy)benzaldehyde (41). Method B was followed on a 0.23 mmol scale starting from 3-iodophenol **39** and organobismuthine **21b**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **41** as a yellow oil (33 mg, 44%): R_f 0.69 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.64 (dt, J = 7.4, 1.1 Hz, 1H), 7.52–7.46 (m, 3H), 7.37 (t, J = 2.0 Hz, 1H), 7.28 (ddd, J = 8.1, 2.5, 1.0 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.99 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 157.7, 157.1, 138.3, 133.3, 131.4, 130.8, 128.4, 125.5, 125.0, 118.7, 118.6, 94.5; IR (neat) 3059, 2923, 2827, 2734, 1697, 1572, 1465, 1450, 1243, 1208, 846, 781; HRMS (ESI) calcd for $[C_{13}H_9IO_2 + H]^+$: 324.9720, found 324.9714.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00767.

Crystallographic data for **1f**, **1i**, **1k**, **1n**, **1s**, **1t**, **17a**, **21c**, and **21e** (ZIP)

Copies of ^{1}H, ^{13}C, and IR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Supporting Information

Synthesis of Highly Functionalized Triarylbismuthines by Functional Group Manipulation and Use in Palladium- and Copper-Catalyzed Arylation Reactions

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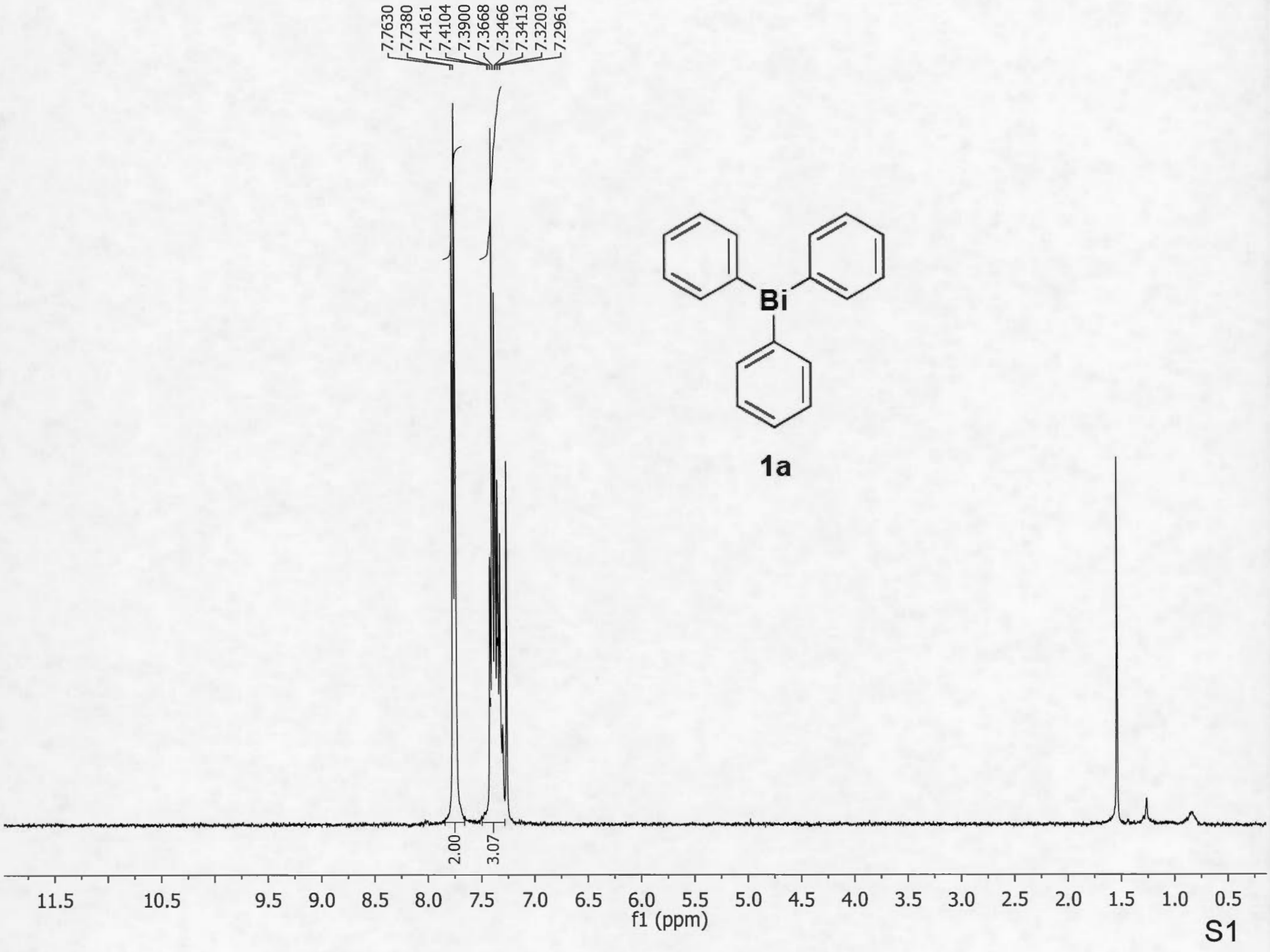
Spectral data: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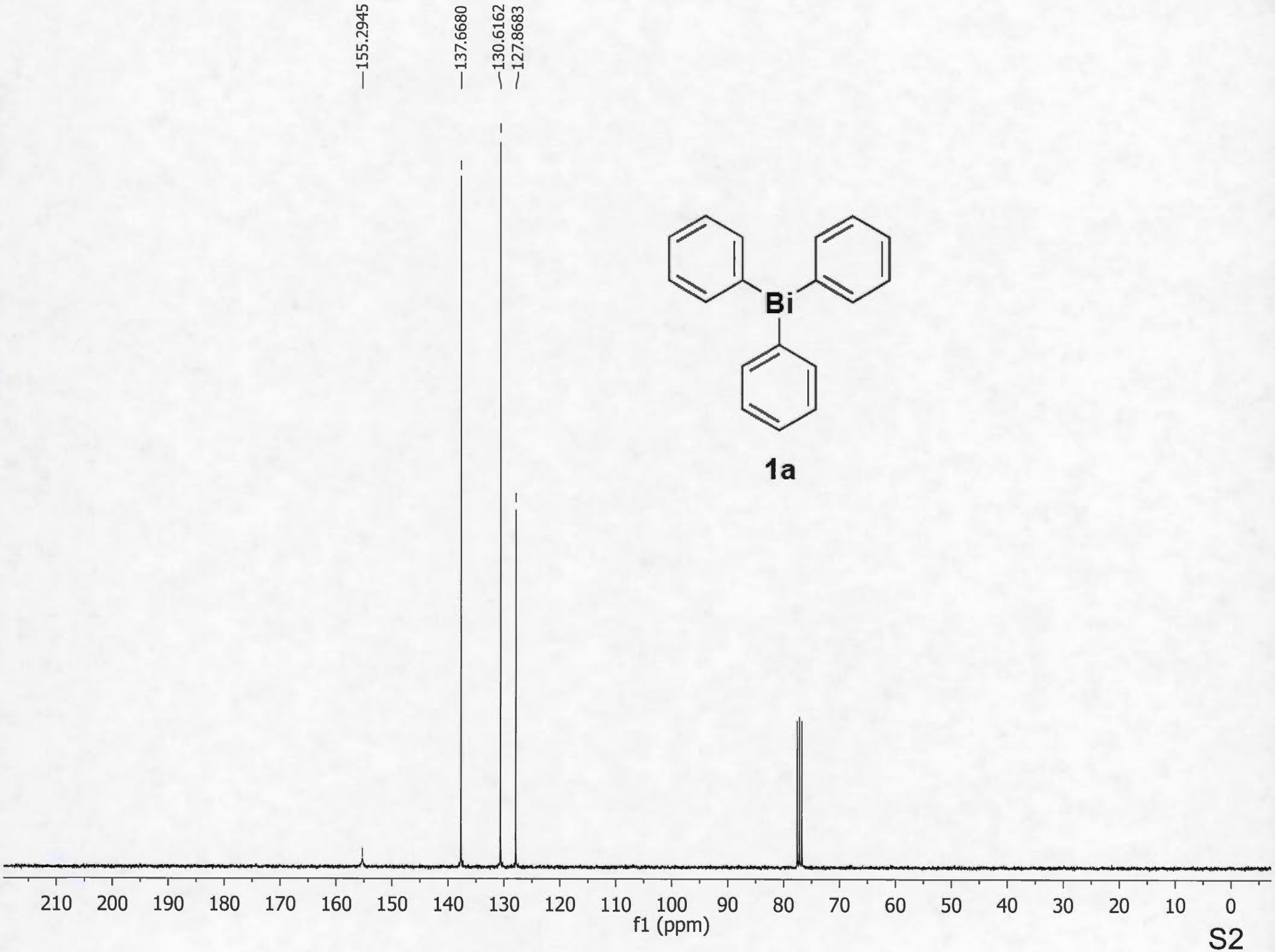
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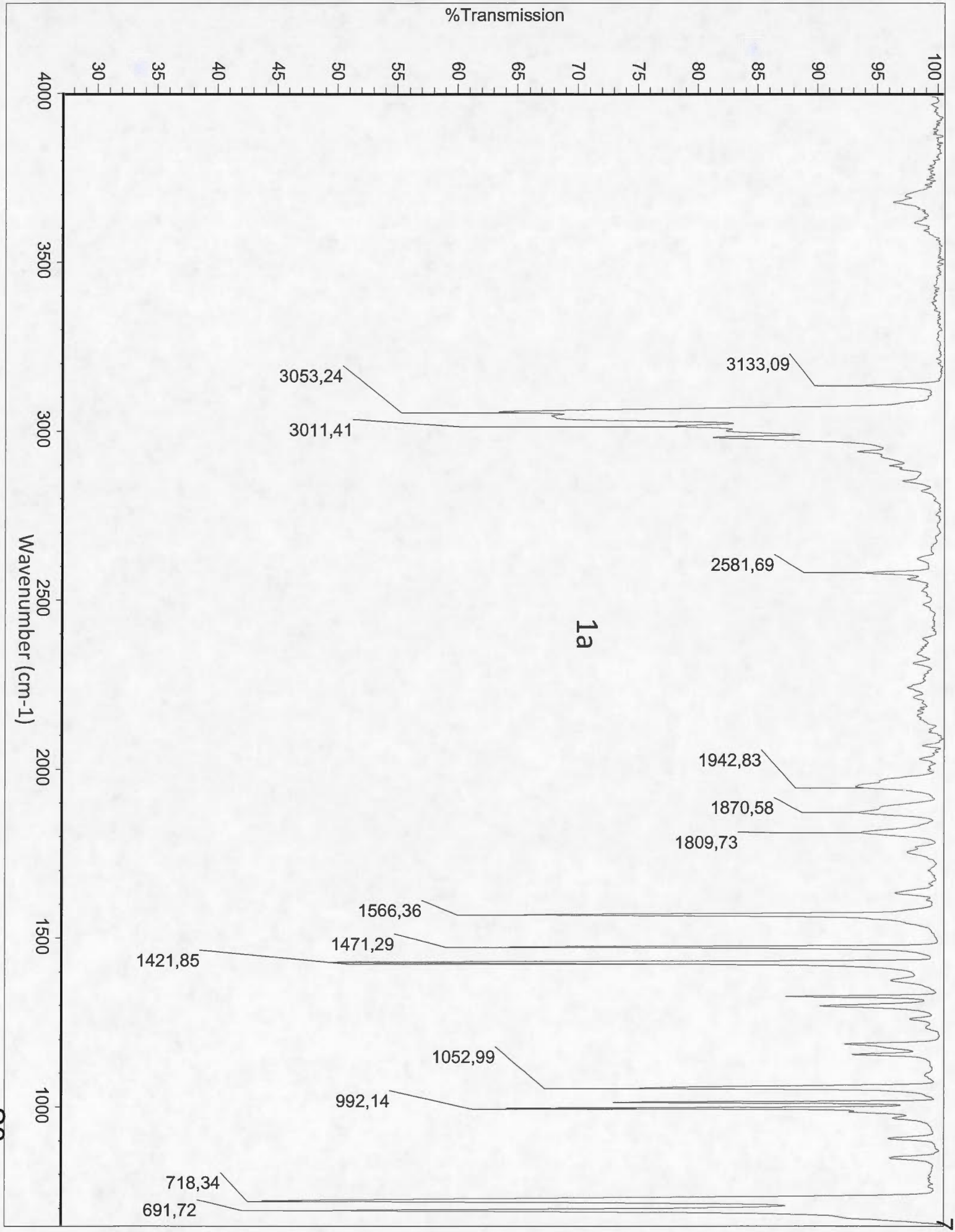
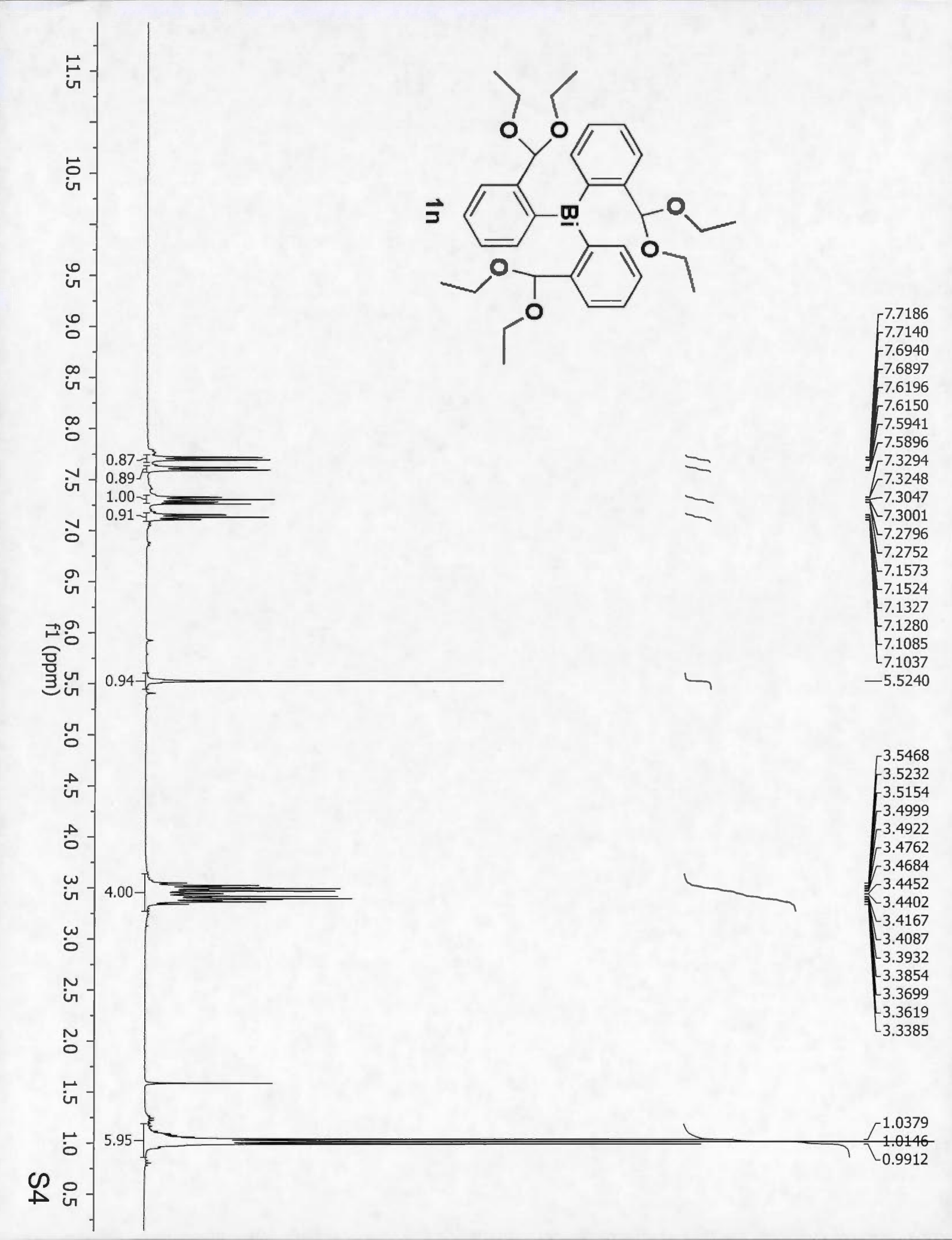
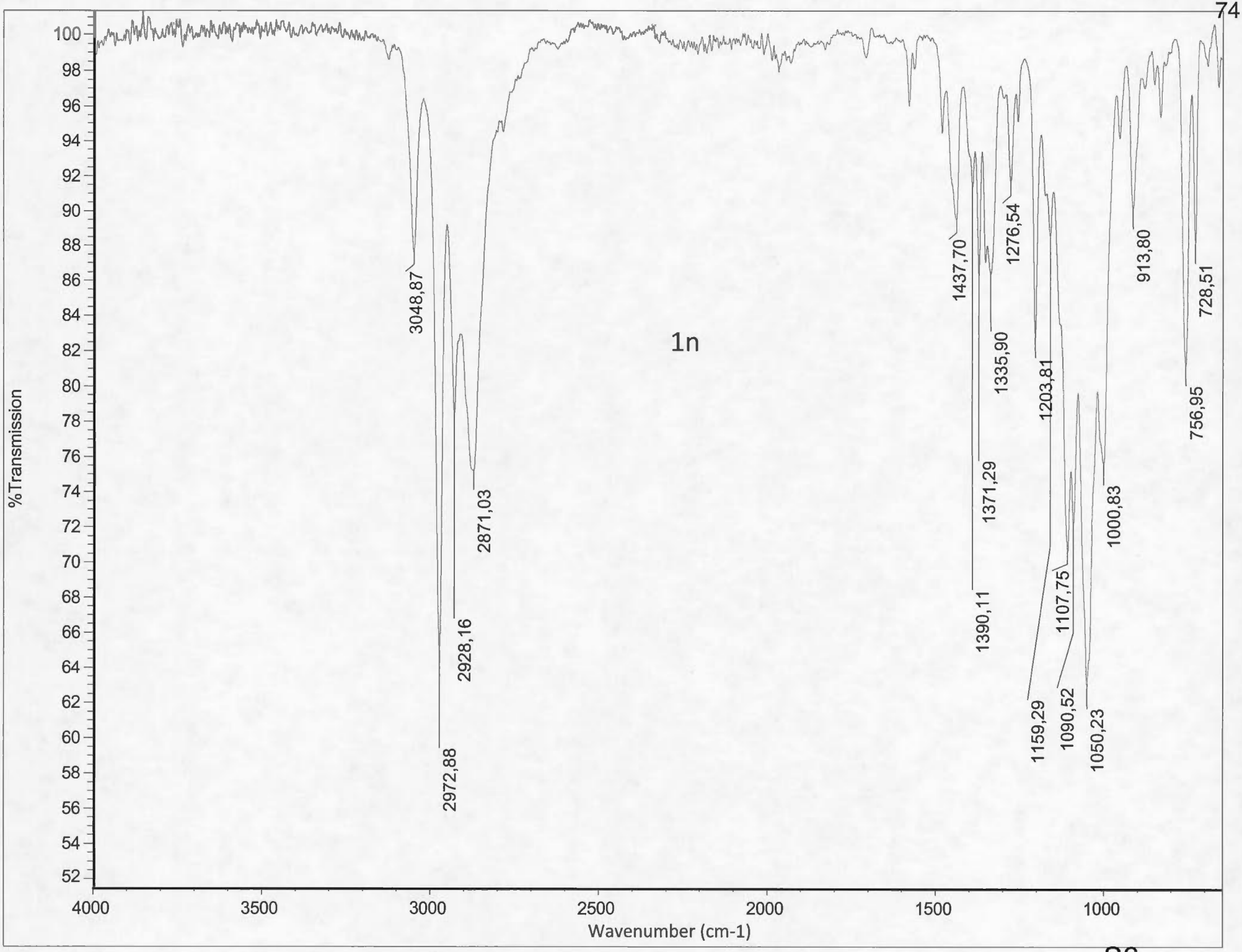
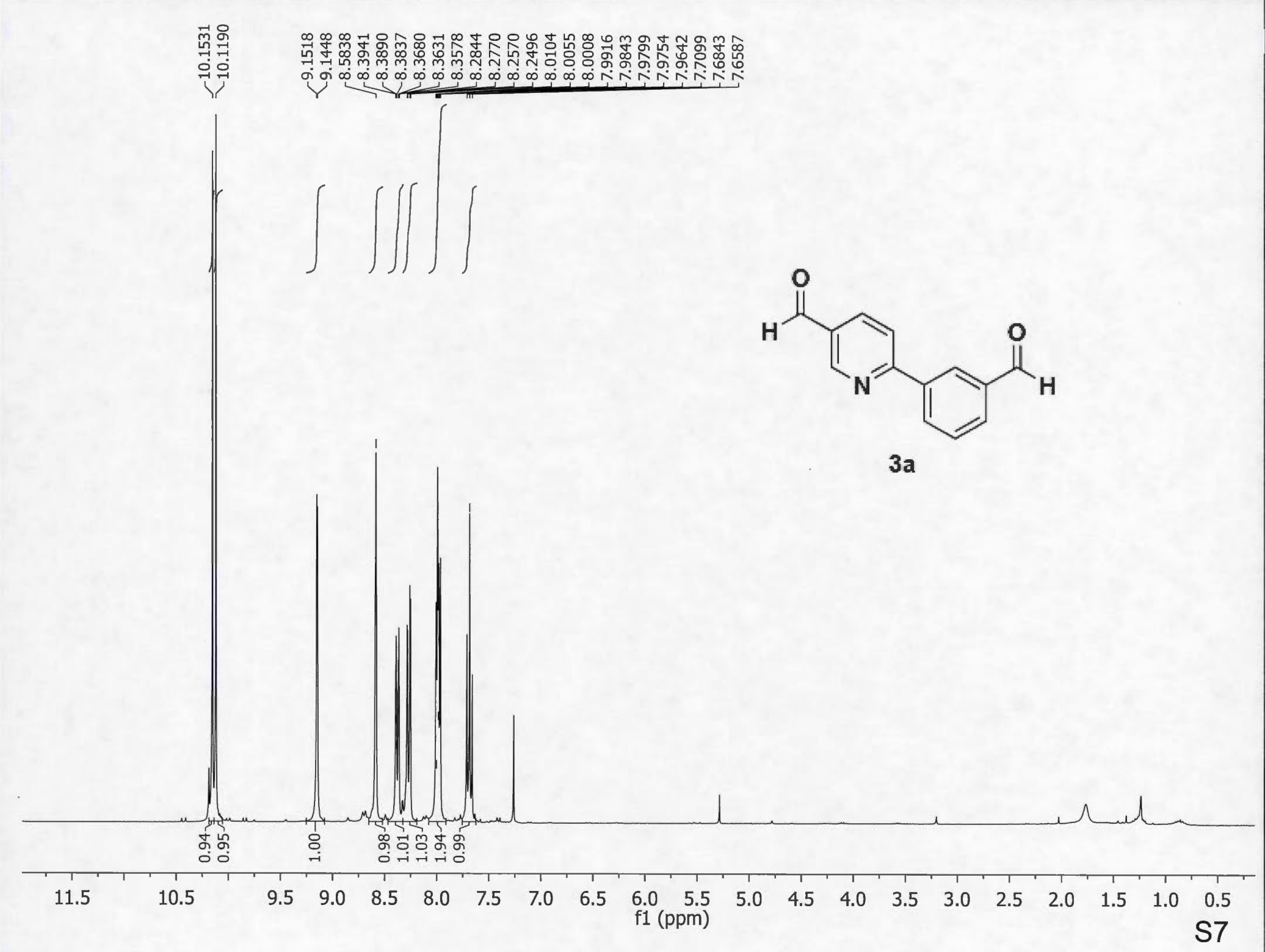
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

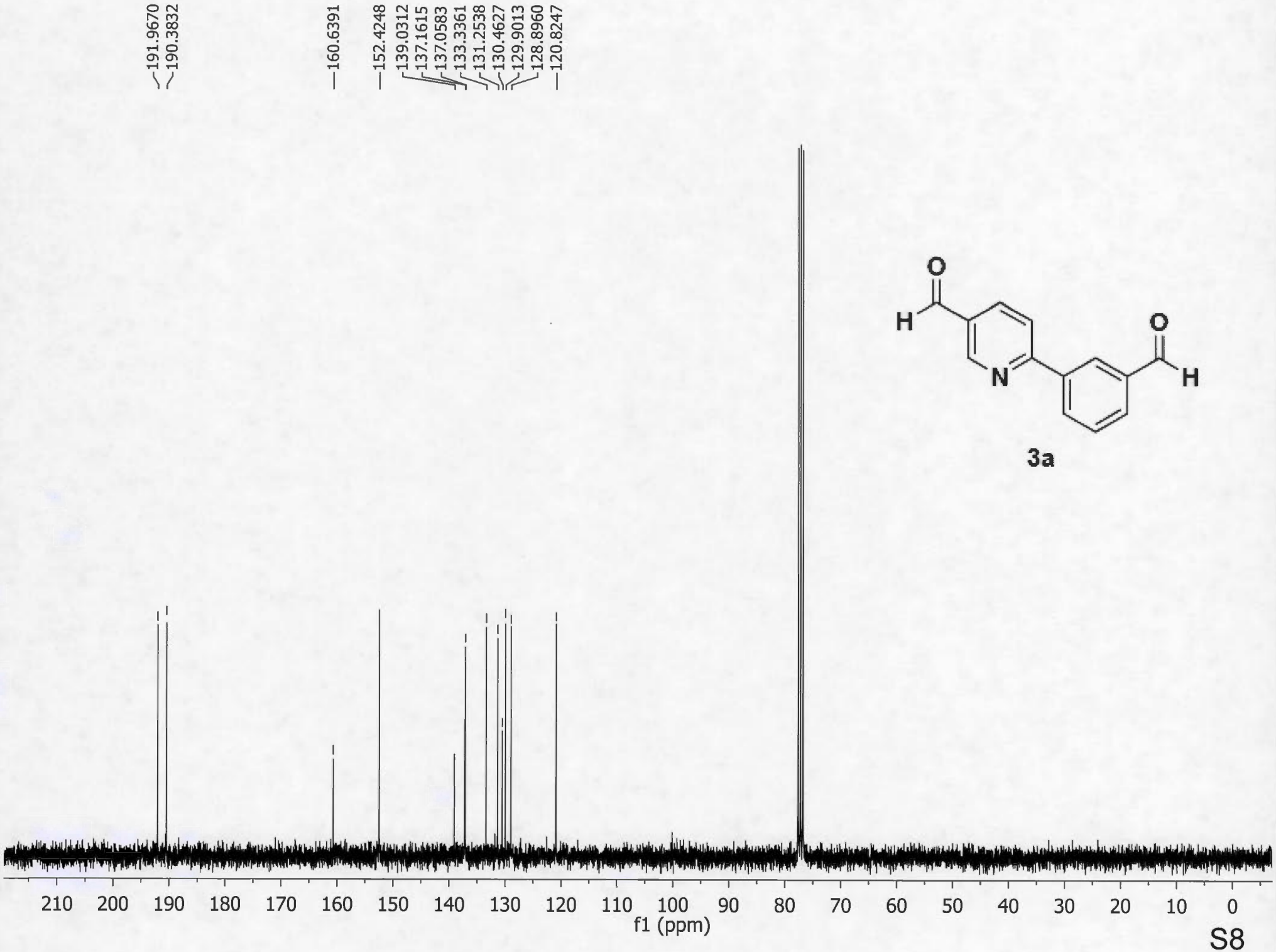

%Transmission
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
3133,09
3053,24
3011,41
2581,69
1942,83
1870,58
1809,73
1566,36
1471,29
1421,85
1052,99
992,14
718,34
691,72
1a

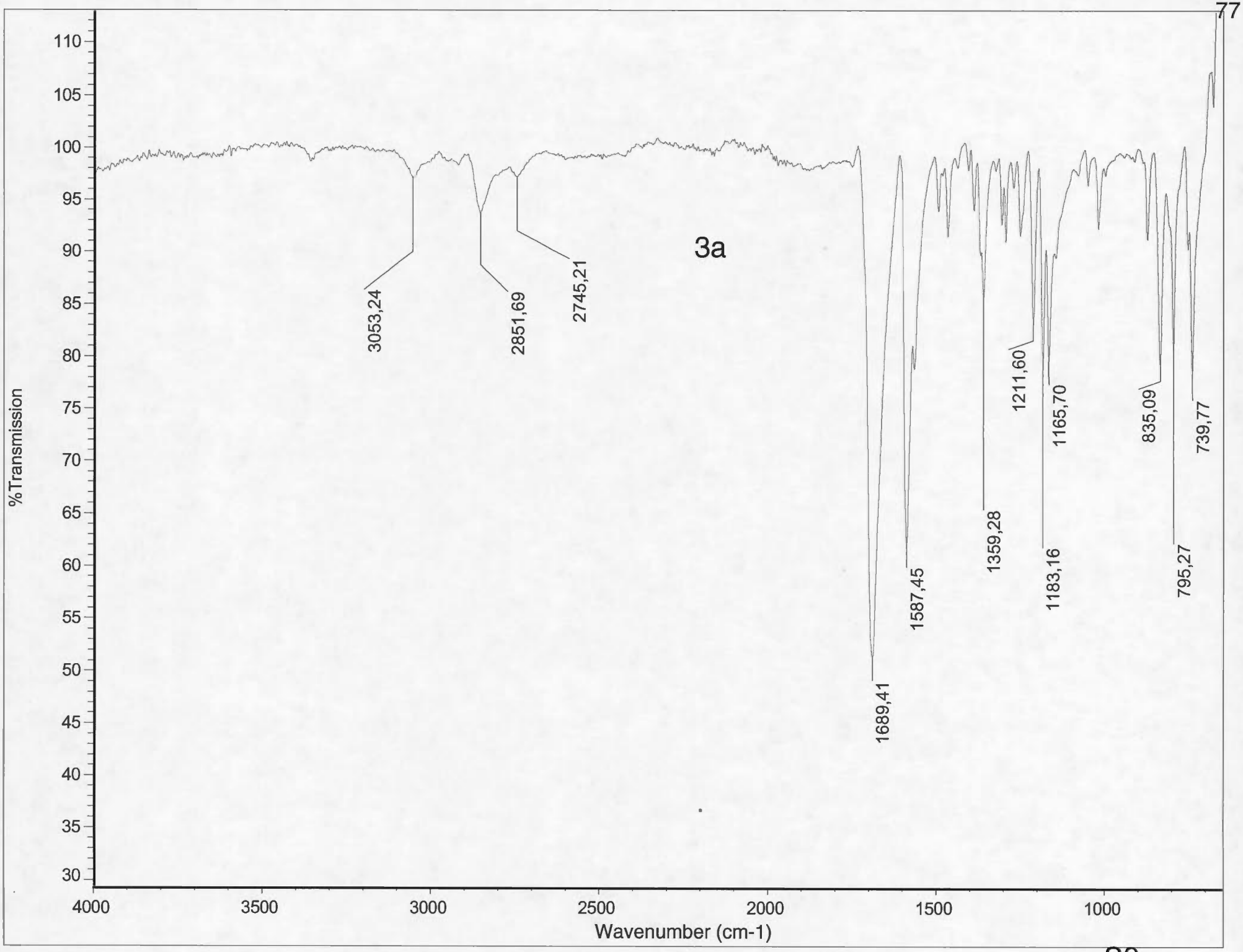

1n
Bi
O
O
O
O
O
O
f1 (ppm)
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.87
0.89
1.00
0.91
0.94
4.00
5.95
7.7186
7.7140
7.6940
7.6897
7.6196
7.6150
7.5941
7.5896
7.3294
7.3248
7.3047
7.3001
7.2796
7.2752
7.1573
7.1524
7.1327
7.1280
7.1085
7.1037
5.5240
3.5468
3.5232
3.5154
3.4999
3.4922
3.4762
3.4684
3.4452
3.4402
3.4167
3.4087
3.3932
3.3854
3.3699
3.3619
3.3385
1.0379
1.0146
0.9912

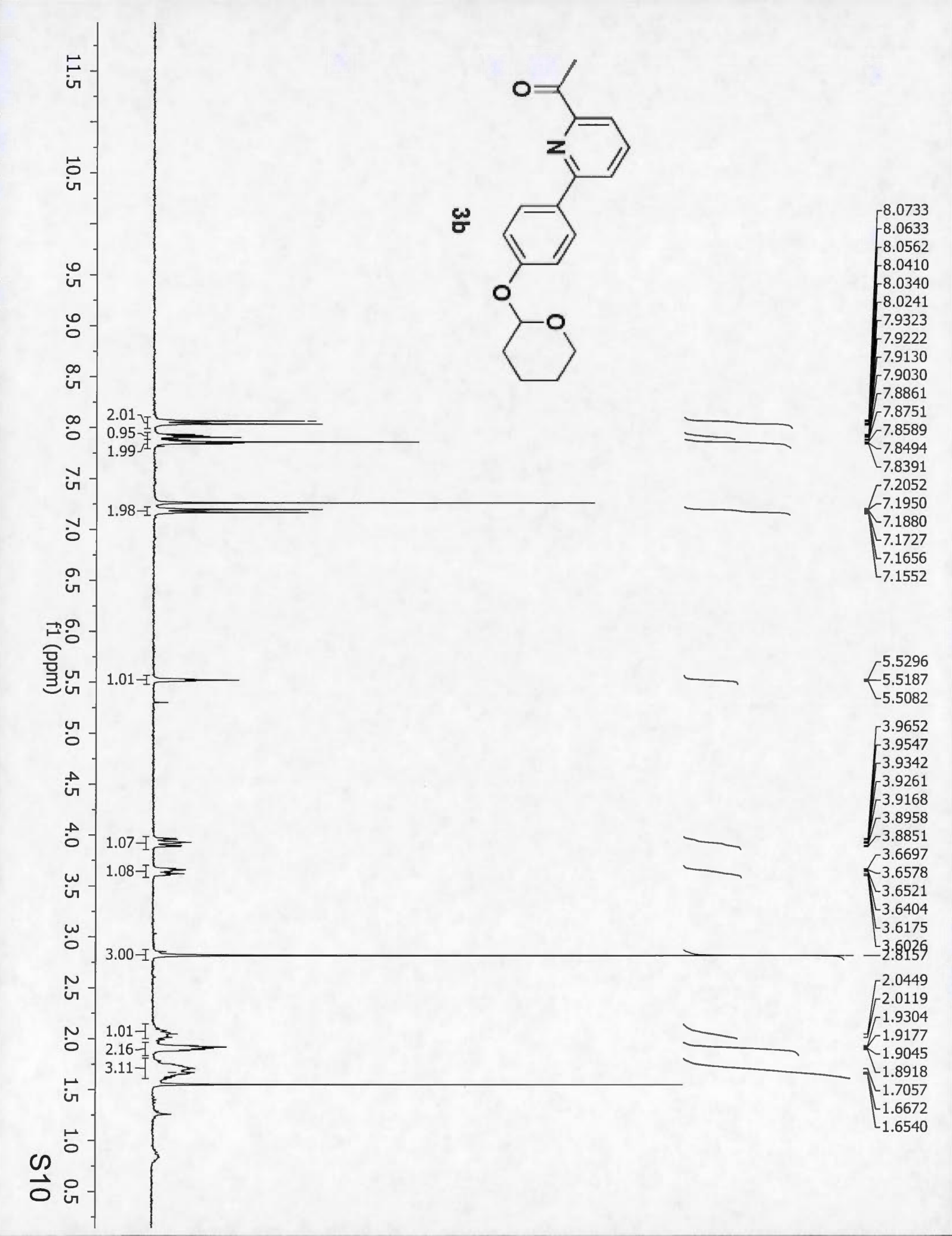
1n
Bi
O
O
O
O
O
O
162.5645
144.4847
140.6403
130.9745
127.5235
126.7799
104.3593
61.4381
15.0775
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

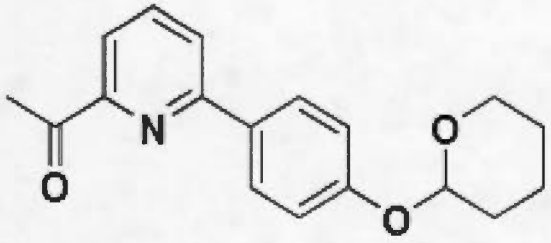

1n
%Transmission
Wavenumber (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
3048,87
2972,88
2928,16
2871,03
1437,70
1390,11
1371,29
1335,90
1276,54
1203,81
1159,29
1107,75
1090,52
1050,23
1000,83
913,80
756,95
728,51


10.1531
10.1190
9.1518
9.1448
8.5838
8.3941
8.3890
8.3837
8.3680
8.3631
8.3578
8.2844
8.2770
8.2570
8.2496
8.0104
8.0055
8.0008
7.9916
7.9843
7.9799
7.9754
7.9642
7.7099
7.6843
7.6587
O
H
N
O
H
3a
0.94
0.95
1.00
0.98
1.01
1.03
1.94
0.99
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


191.9670
190.3832
160.6391
152.4248
139.0312
137.1615
137.0583
133.3361
131.2538
130.4627
129.9013
128.8960
120.8247
O
H
N
O
H
3a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


3a
%Transmission
Wavenumber (cm-1)
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
2000
1500
1000
3053,24
2851,69
2745,21
1689,41
1587,45
1359,28
1211,60
1183,16
1165,70
835,09
795,27
739,77

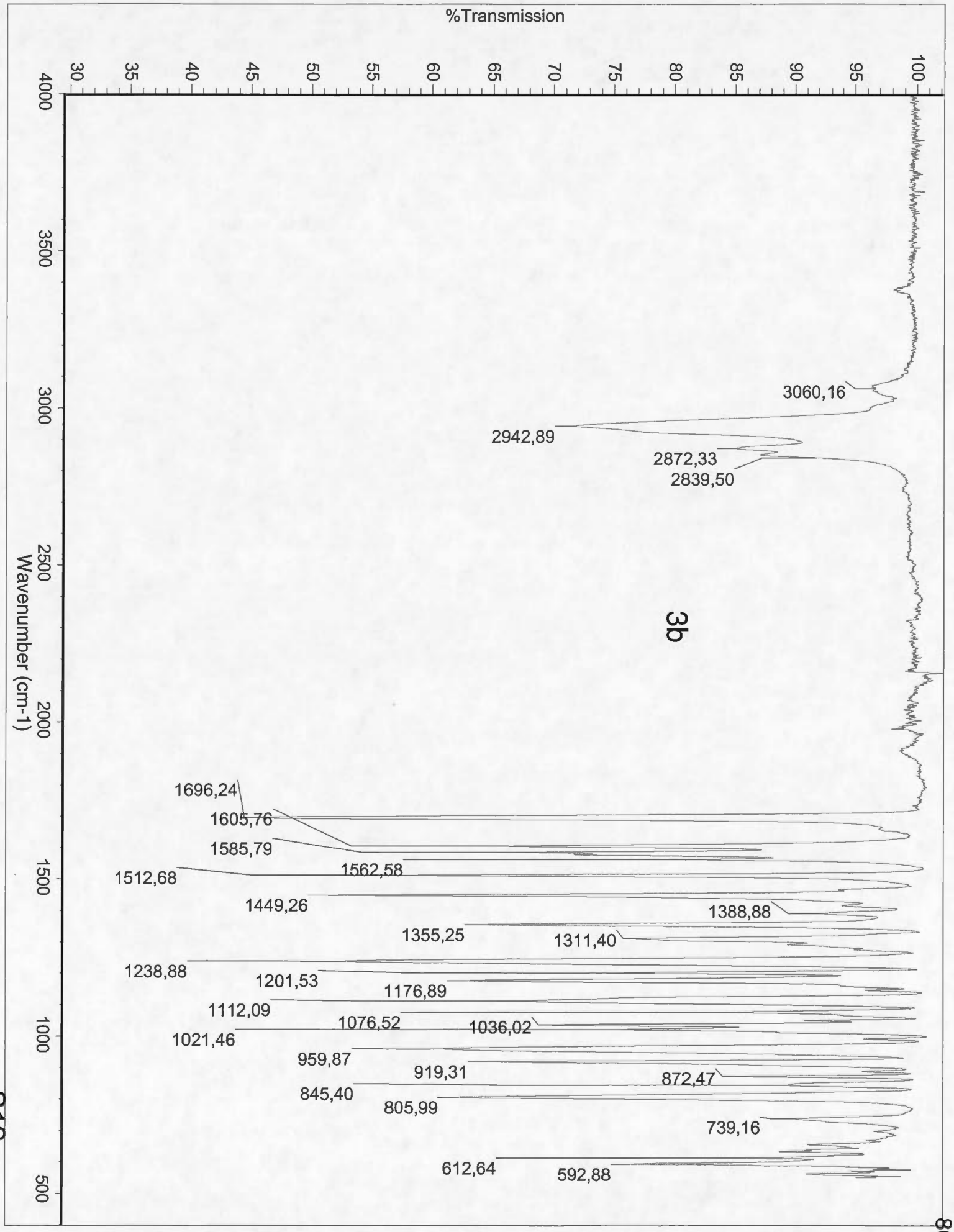

3b
f1 (ppm)
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
2.01
0.95
1.99
1.98
1.01
1.07
1.08
3.00
1.01
2.16
3.11
8.0733
8.0633
8.0562
8.0410
8.0340
8.0241
7.9323
7.9222
7.9130
7.9030
7.8861
7.8751
7.8589
7.8494
7.8391
7.2052
7.1950
7.1880
7.1727
7.1656
7.1552
5.5296
5.5187
5.5082
3.9652
3.9547
3.9342
3.9261
3.9168
3.8958
3.8851
3.6697
3.6578
3.6521
3.6404
3.6175
3.6026
2.8157
2.0449
2.0119
1.9304
1.9177
1.9045
1.8918
1.7057
1.6672
1.6540

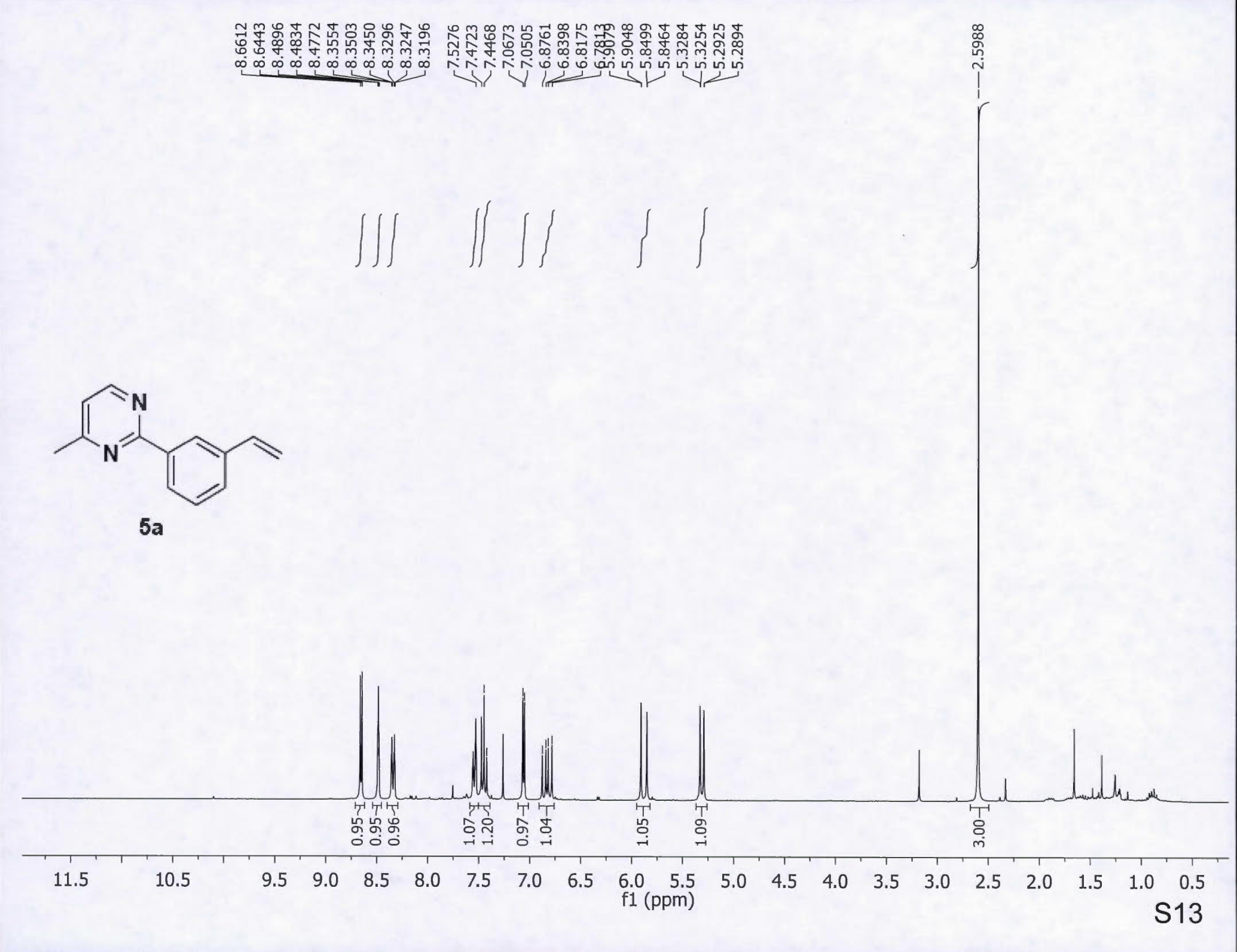


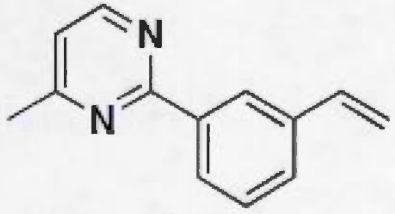
3b

200.9109
158.4606
156.3637
153.4336
137.6431
131.9720
128.2623
122.9302
119.2577
116.8180
96.3907
62.2047
30.4365
25.9492
25.3325
18.8470

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

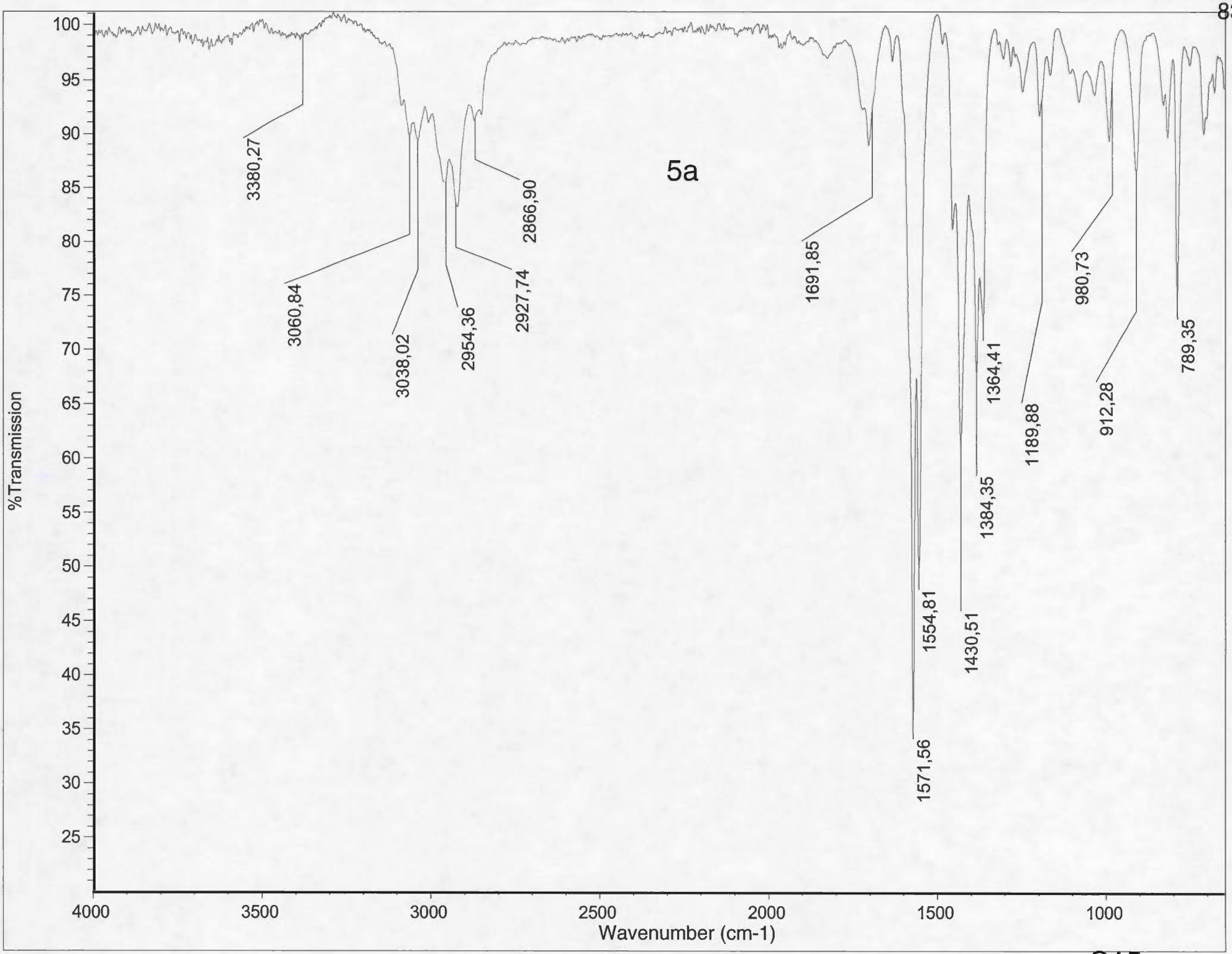

%Transmission
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)
3060,16
2942,89
2872,33
2839,50
1696,24
1605,76
1585,79
1562,58
1512,68
1449,26
1388,88
1355,25
1311,40
1238,88
1201,53
1176,89
1112,09
1076,52
1036,02
1021,46
959,87
919,31
872,47
845,40
805,99
739,16
612,64
592,88
3b

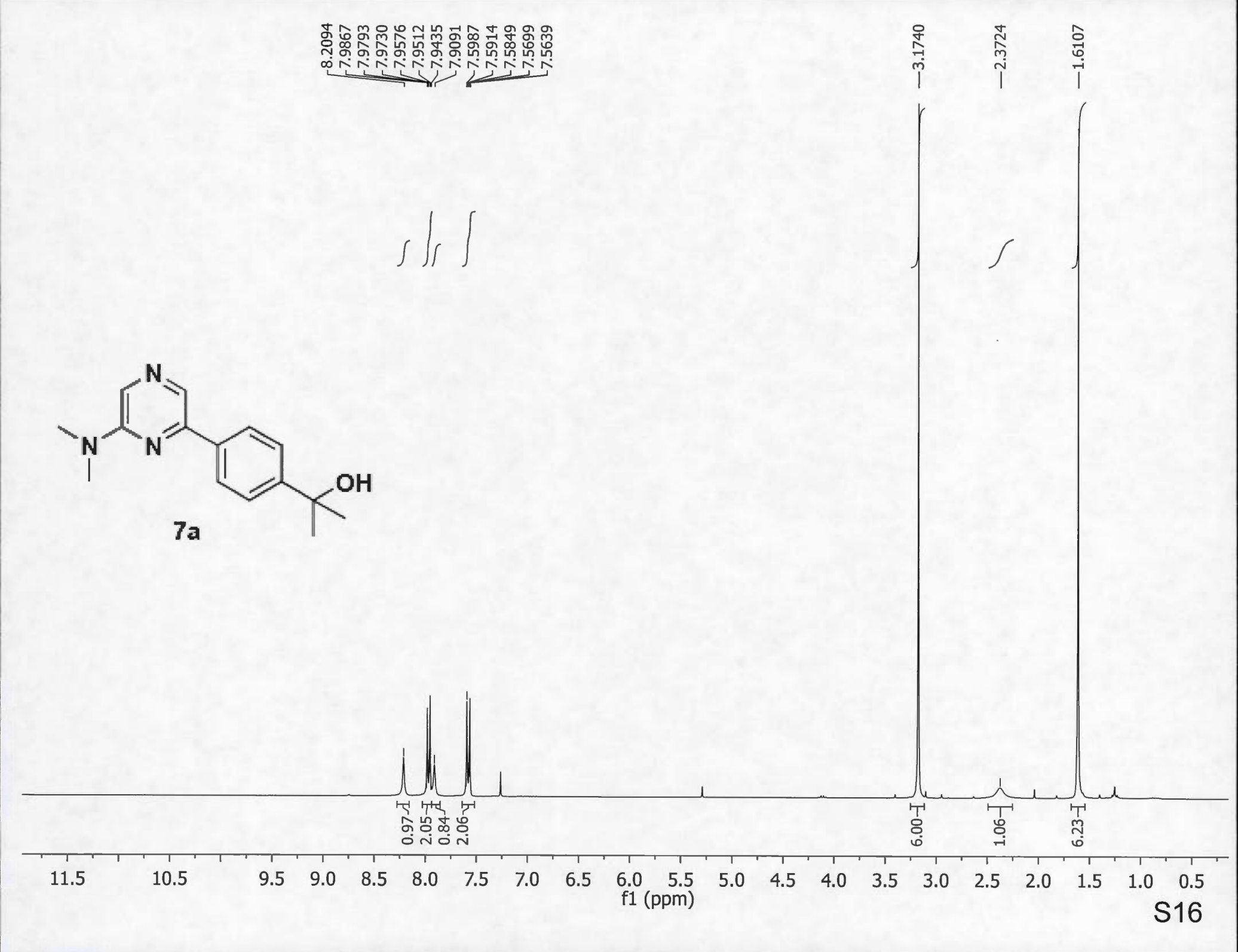

8.6612
8.6443
8.4896
8.4834
8.4772
8.3554
8.3503
8.3450
8.3296
8.3247
8.3196
7.5276
7.4723
7.4468
7.0673
7.0505
6.8761
6.8398
6.8175
6.7813
5.9079
5.9048
5.8499
5.8464
5.3284
5.3254
5.2925
5.2894
2.5988
N
N
5a
0.95
0.95
0.96
1.07
1.20
0.97
1.04
1.05
1.09
3.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



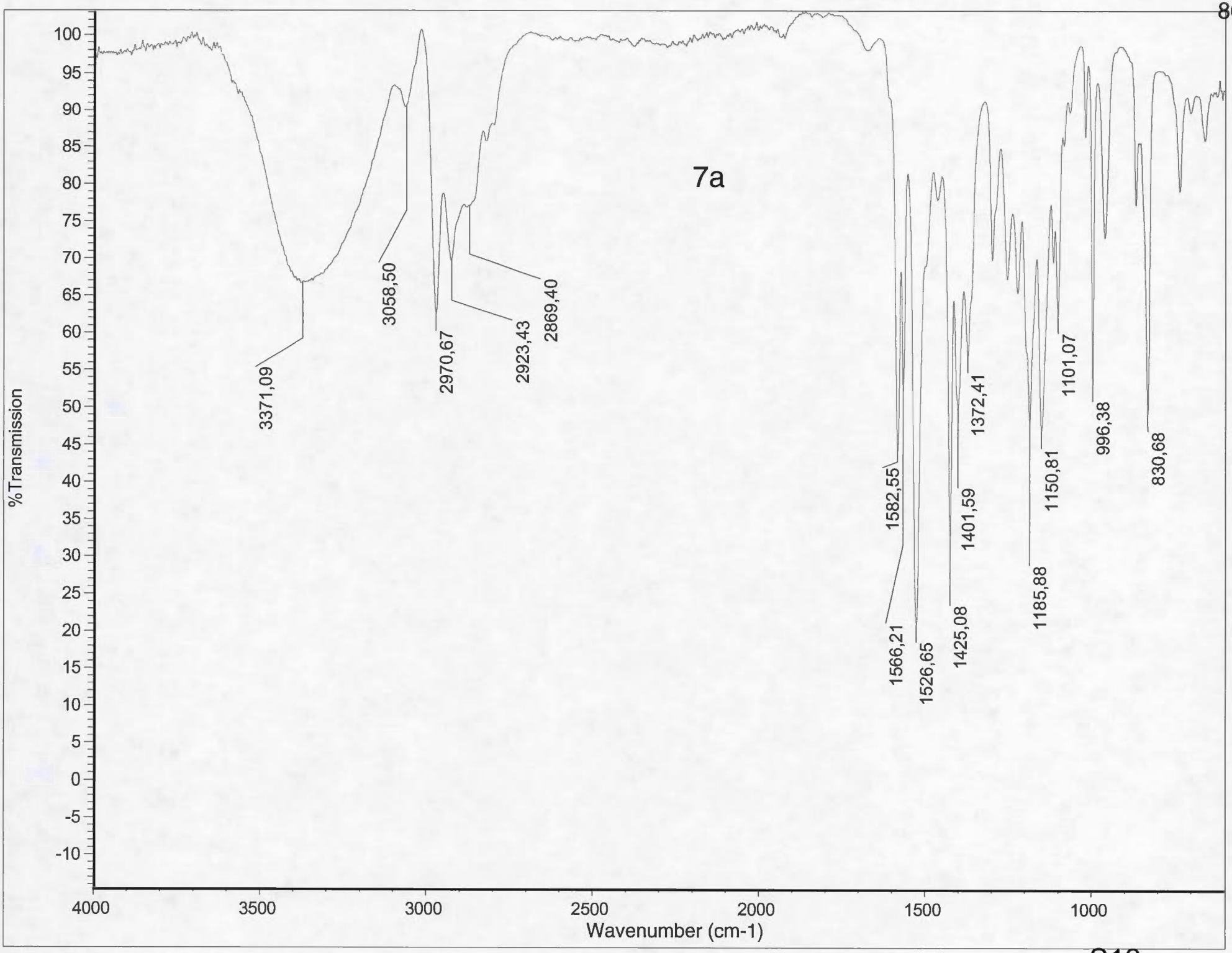
5a

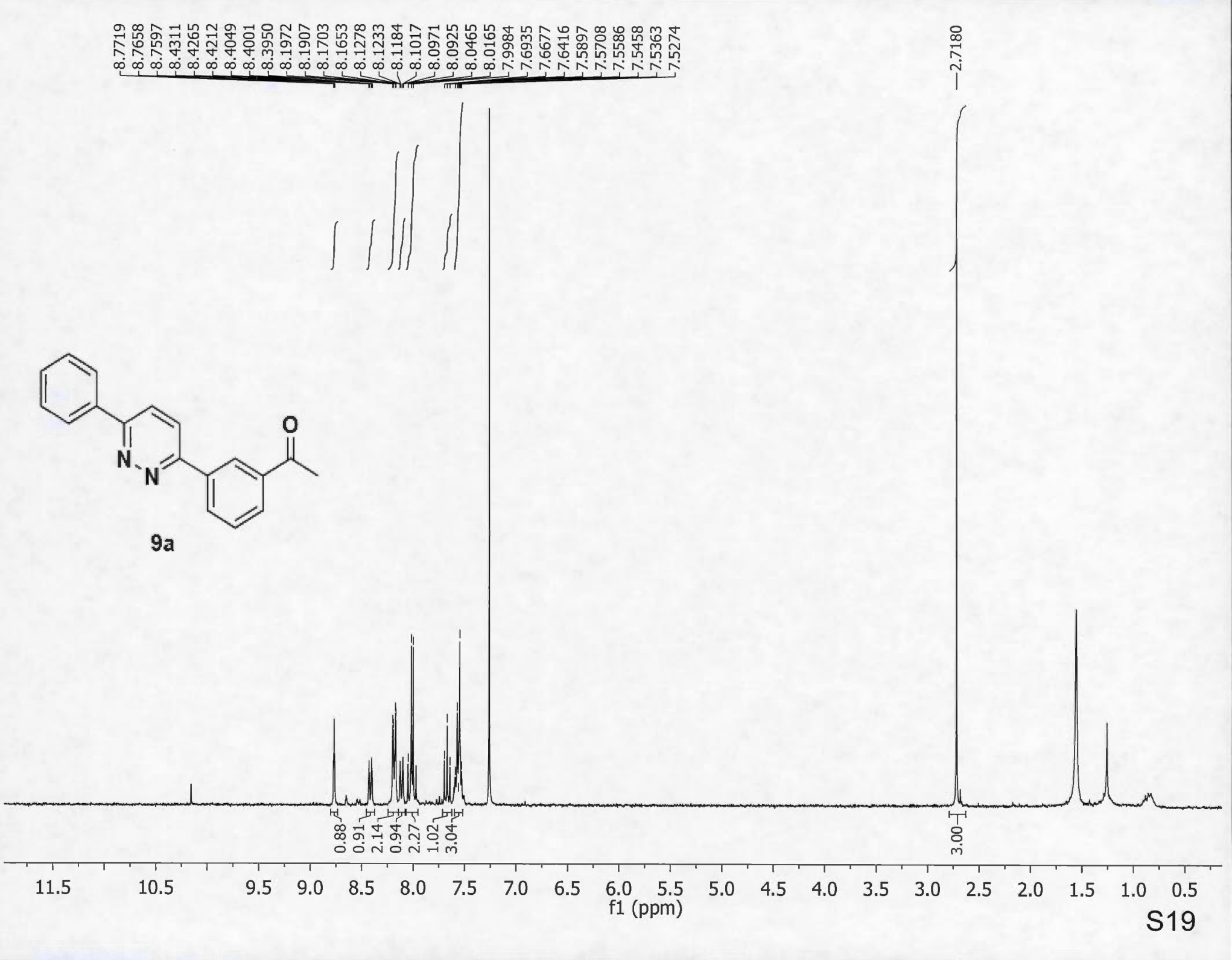
167.4558
164.3440
156.9080
138.2014
138.0082
136.8221
128.8738
128.2634
127.7555
126.2989
118.8564
114.4262
24.5766
f1 (ppm)

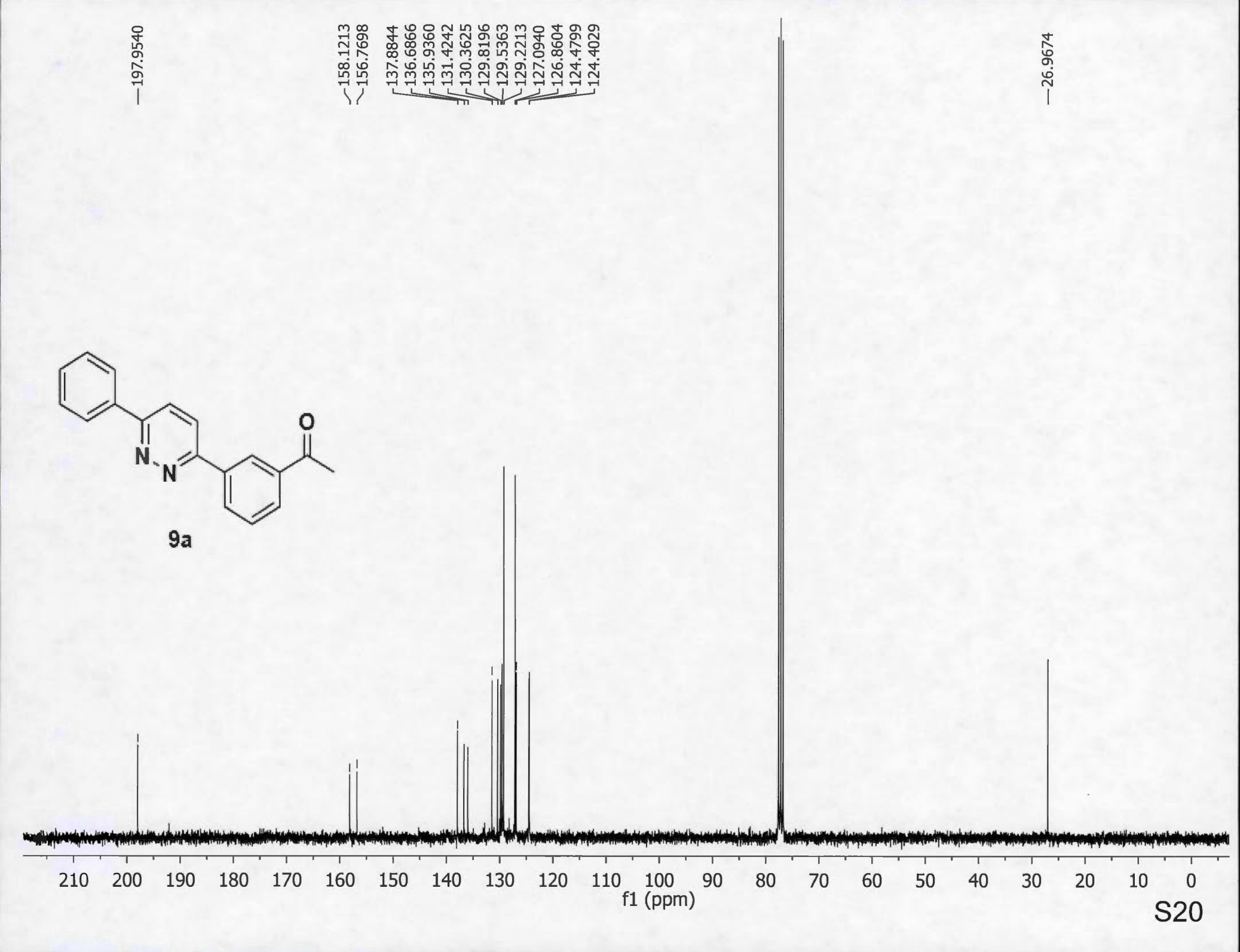

5a
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
4000
3500
3000
2500
2000
1500
1000
3380,27
3060,84
3038,02
2954,36
2927,74
2866,90
1691,85
1571,56
1554,81
1430,51
1384,41
1364,41
1189,88
980,73
912,28
789,35

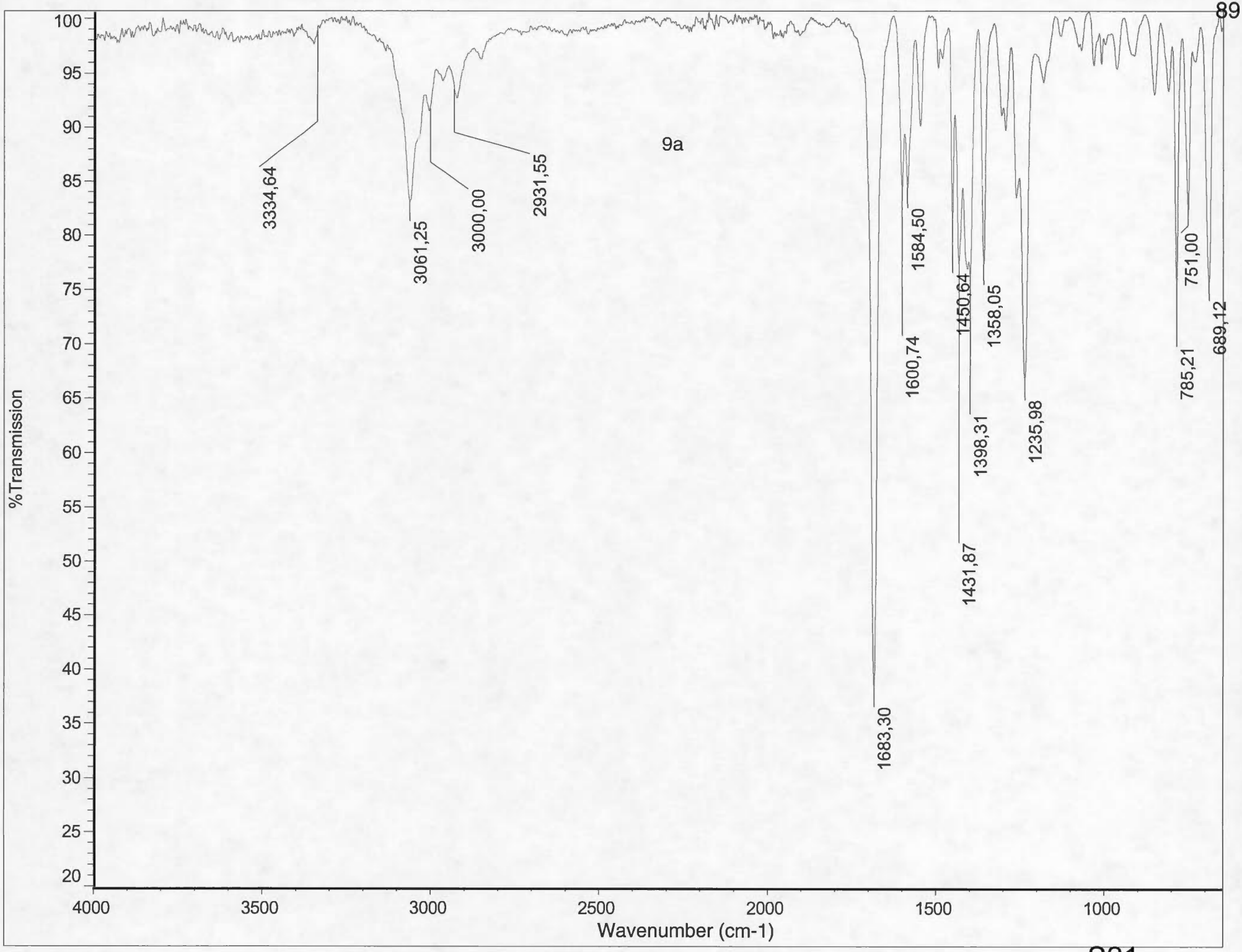

8.2094
7.9867
7.9793
7.9730
7.9576
7.9512
7.9435
7.9091
7.5987
7.5914
7.5849
7.5699
7.5639
3.1740
2.3724
1.6107
N
N
N
OH
7a
0.97
2.05
0.84
2.06
6.00
1.06
6.23
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

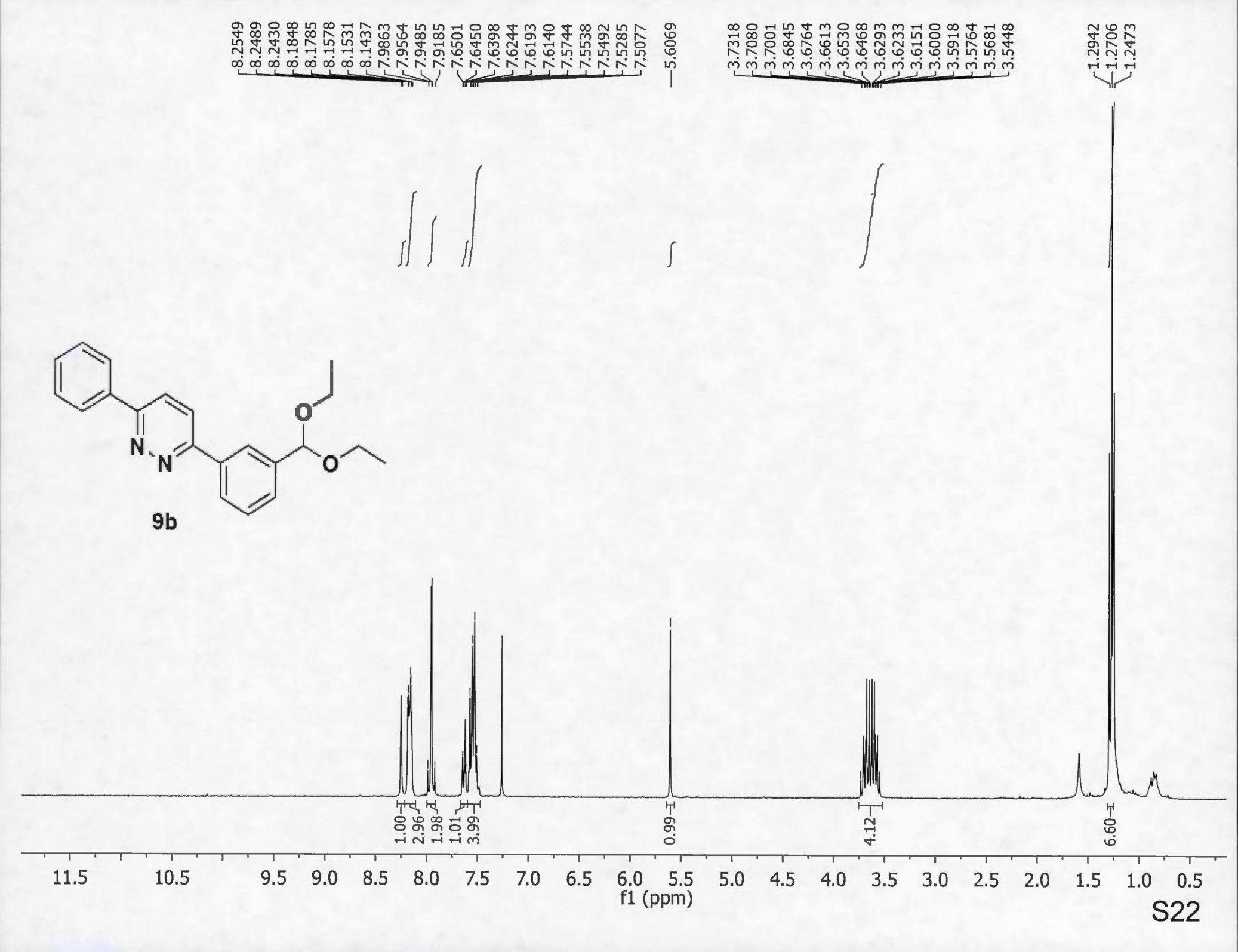
7a
OH
N
N
N
154.3743
150.4803
149.1755
135.9959
128.3571
127.9162
126.8193
124.9594
72.5611
37.6138
31.8552
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

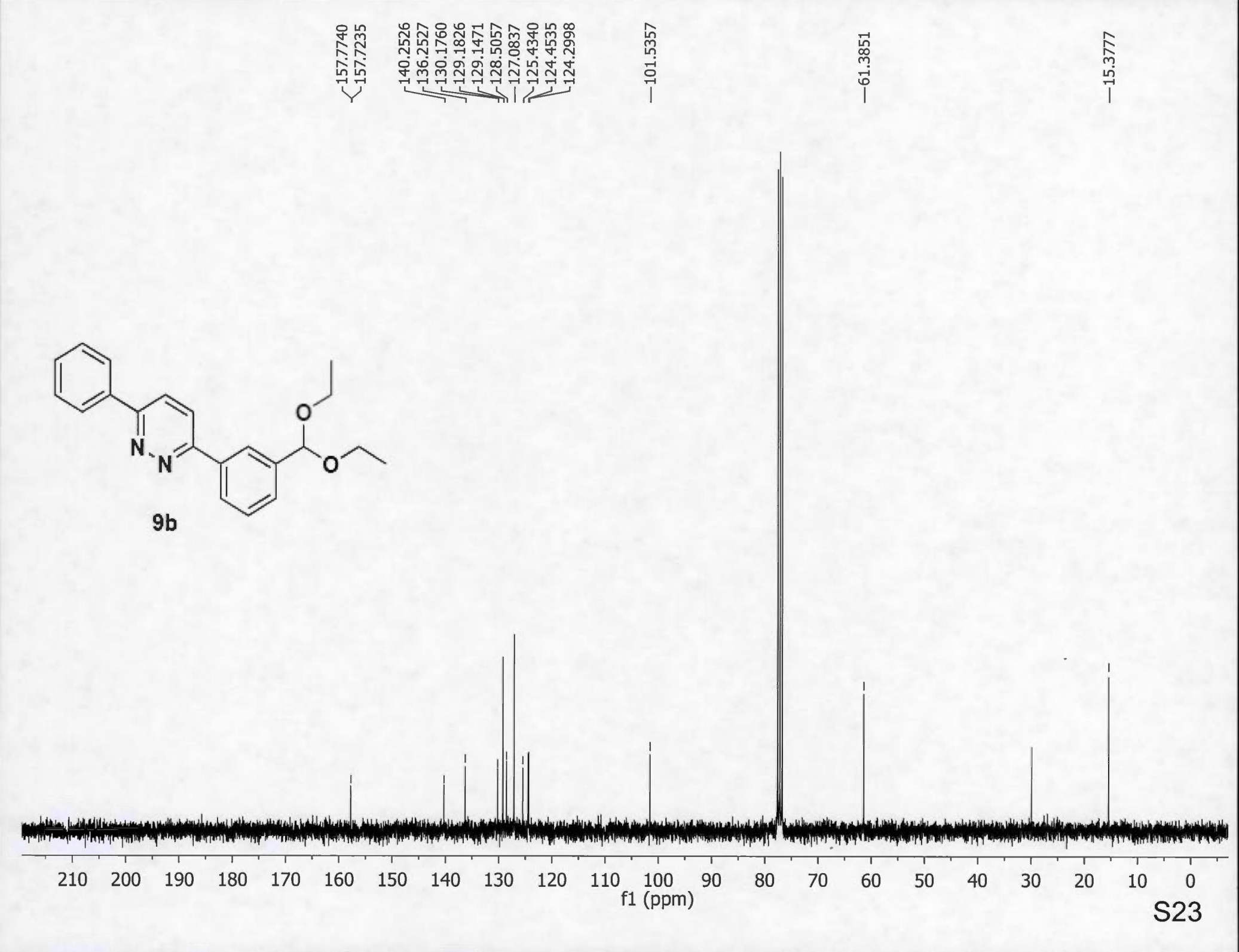

7a
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
4000
3500
3000
2500
2000
1500
1000
3371,09
3058,50
2970,67
2923,43
2869,40
1582,55
1566,21
1526,65
1425,08
1401,59
1372,41
1185,88
1150,81
1101,07
996,38
830,68

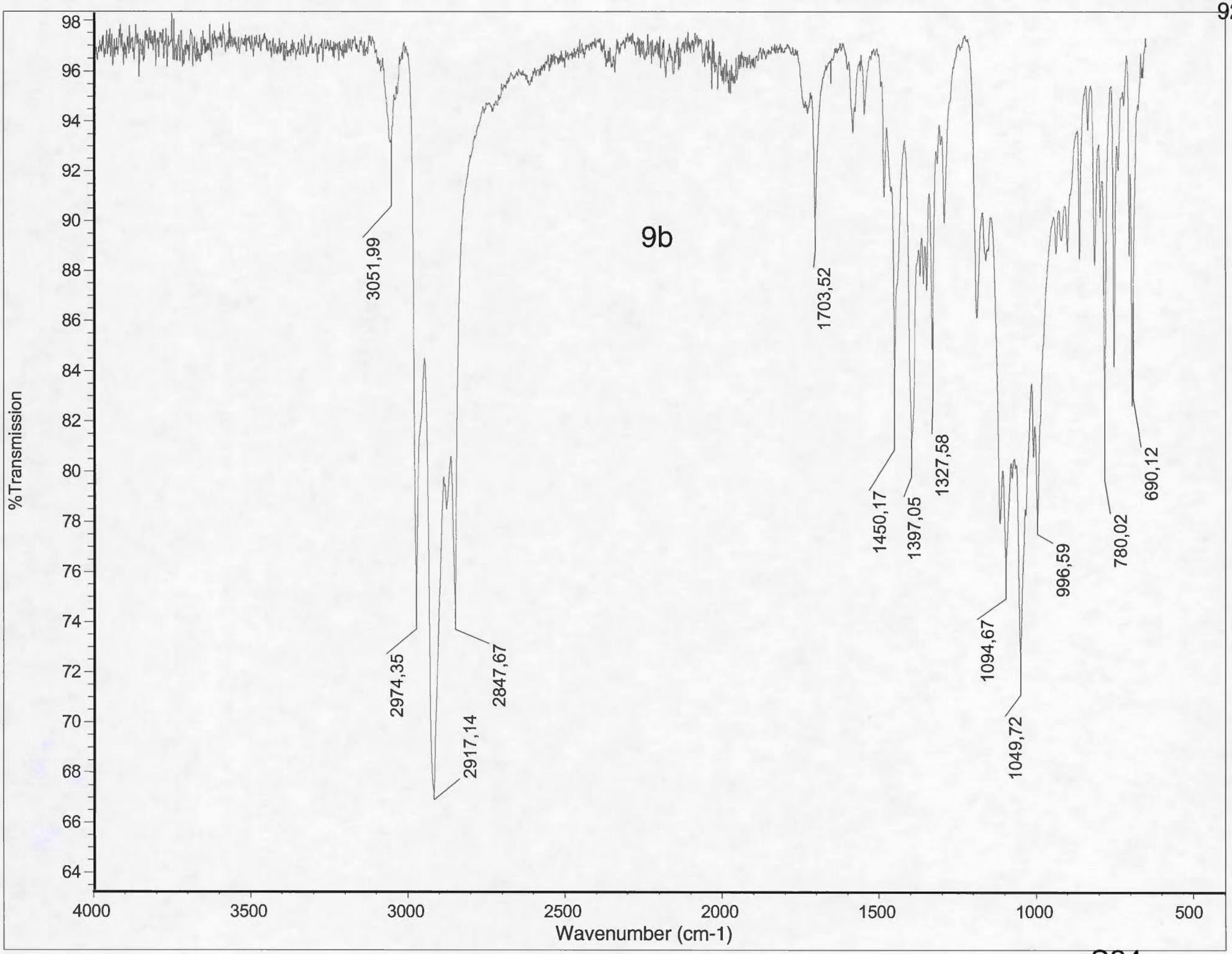

8.7719
8.7658
8.7597
8.4311
8.4265
8.4212
8.4049
8.4001
8.3950
8.1972
8.1907
8.1703
8.1653
8.1278
8.1233
8.1184
8.1017
8.0971
8.0925
8.0465
8.0165
7.9984
7.6935
7.6677
7.6416
7.5897
7.5708
7.5586
7.5458
7.5363
7.5274
2.7180
O
N
N
9a
0.88
0.91
2.14
0.94
2.27
1.02
3.04
3.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

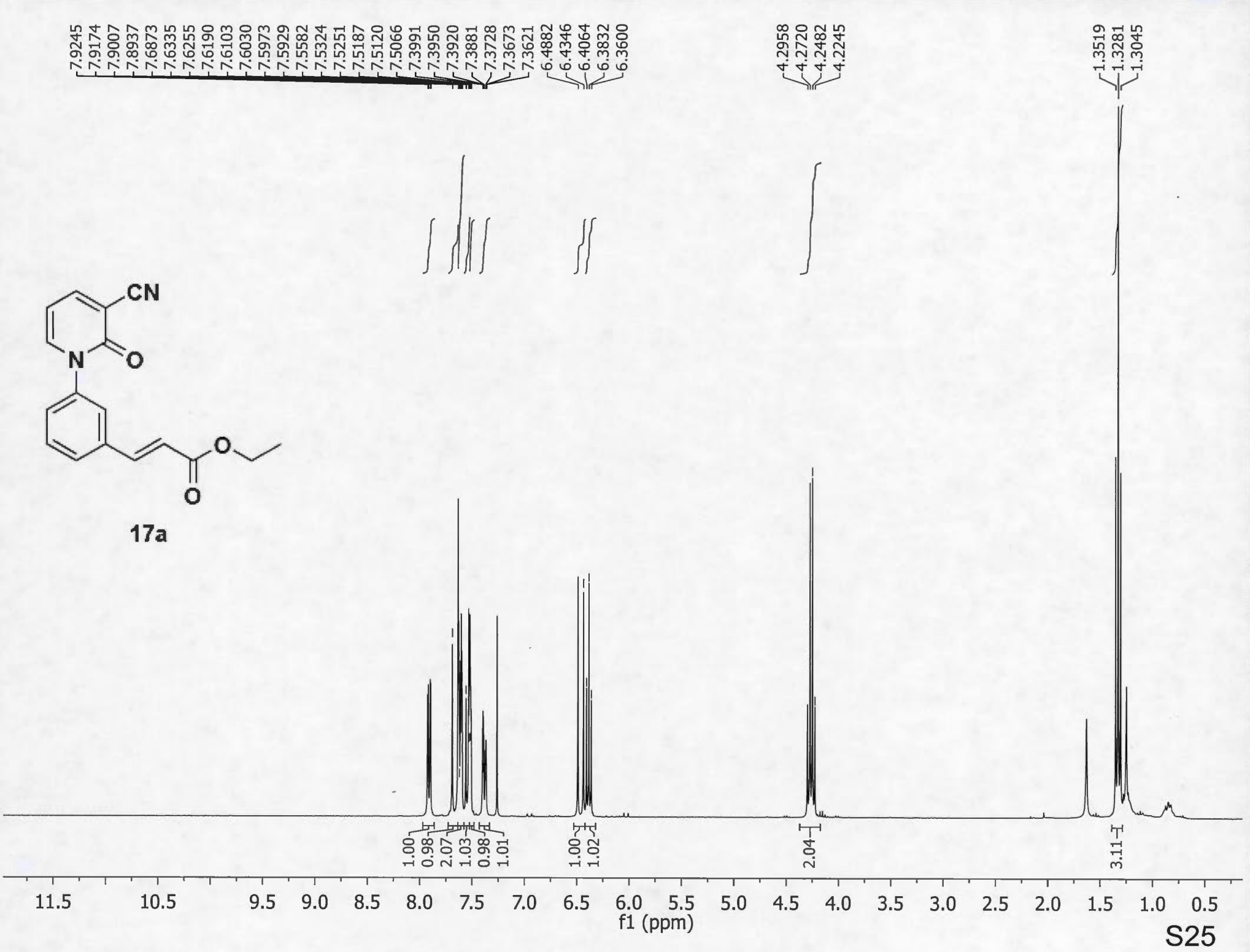

197.9540
158.1213
156.7698
137.8844
136.6866
135.9360
131.4242
130.3625
129.8196
129.5363
129.2213
127.0940
126.8604
124.4799
124.4029
26.9674
O
N
N
9a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

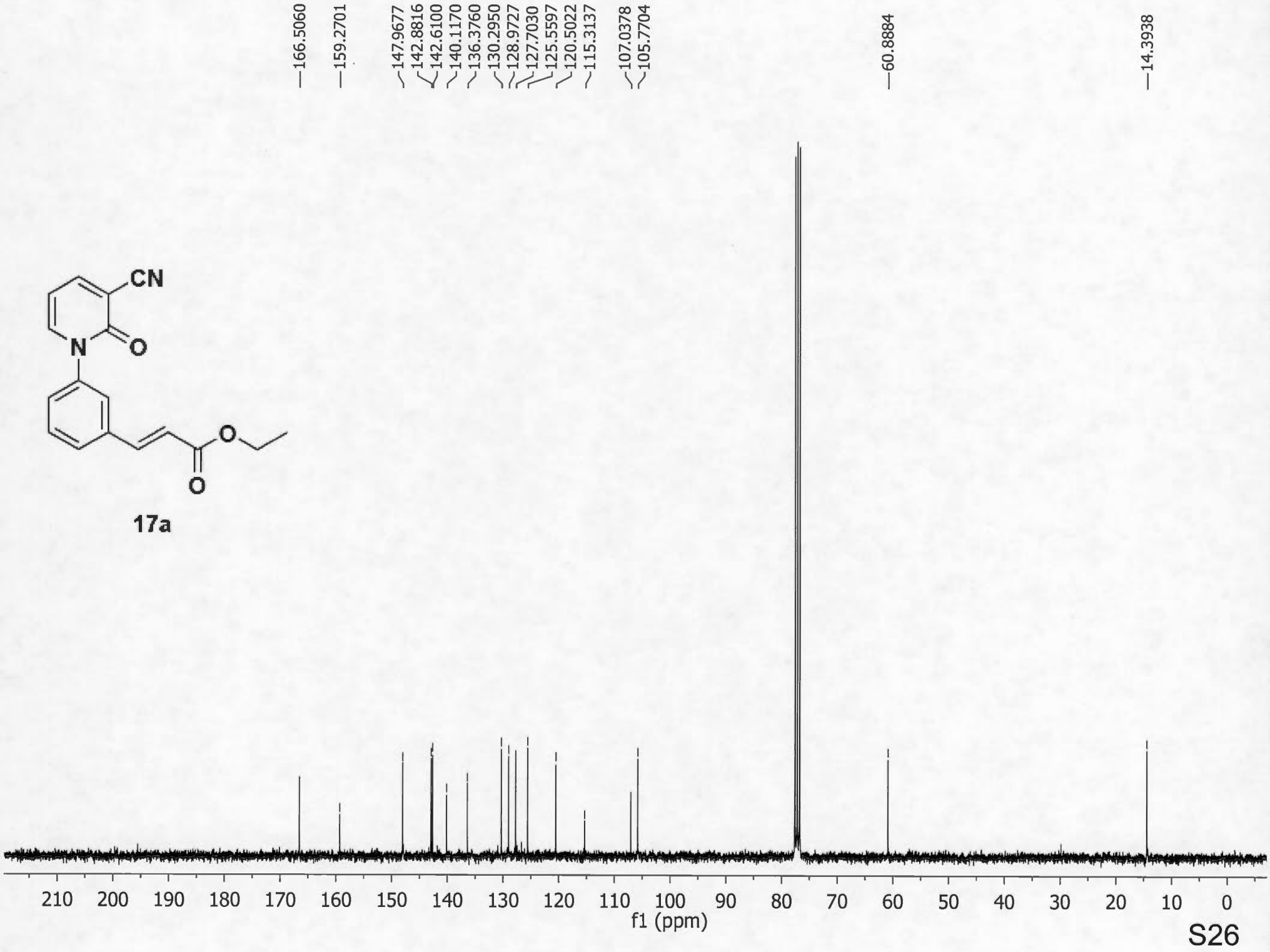

9a
3334,64
3061,25
3000,00
2931,55
1683,30
1600,74
1584,50
1450,64
1431,87
1398,31
1358,05
1235,98
785,21
751,00
689,12
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
4000
3500
3000
2500
2000
1500
1000

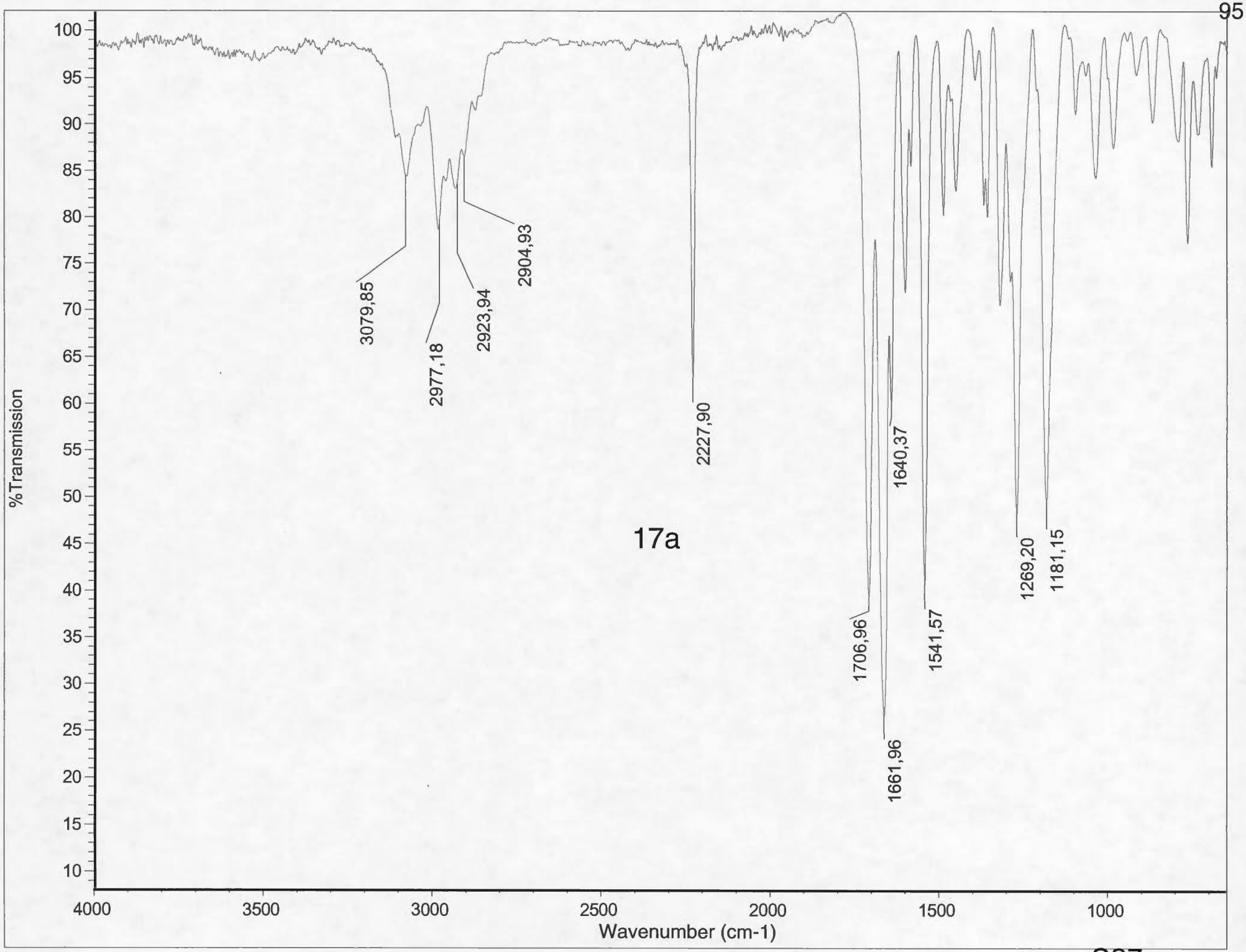

8.2549
8.2489
8.2430
8.1848
8.1785
8.1578
8.1531
8.1437
7.9863
7.9564
7.9485
7.9185
7.6501
7.6450
7.6398
7.6244
7.6193
7.6140
7.5744
7.5538
7.5492
7.5285
7.5077
5.6069
3.7318
3.7080
3.7001
3.6845
3.6764
3.6613
3.6530
3.6468
3.6293
3.6233
3.6151
3.6000
3.5918
3.5764
3.5681
3.5448
1.2942
1.2706
1.2473
N
N
O
O
9b
1.00
2.96
1.98
1.01
3.99
0.99
4.12
6.60
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

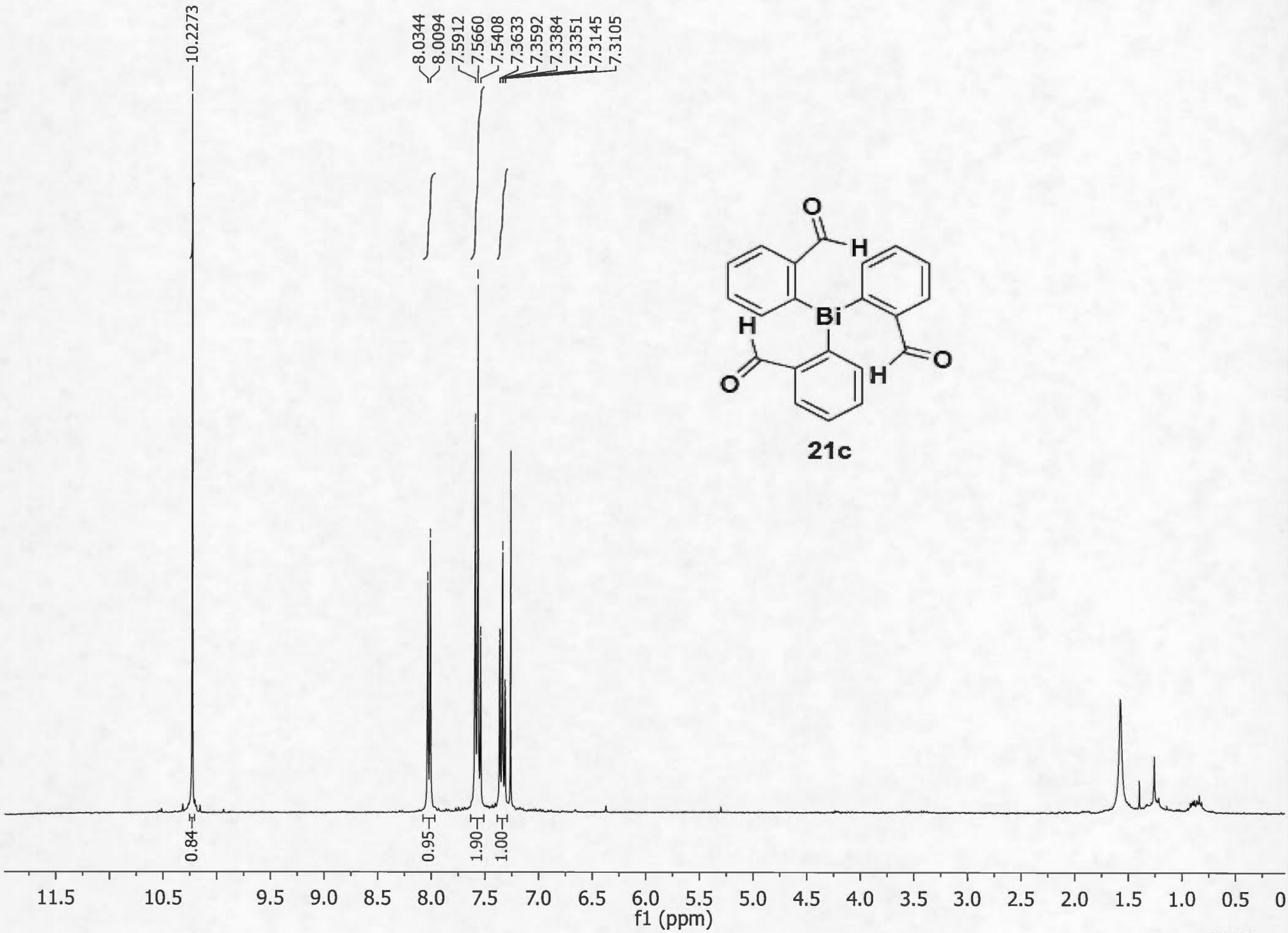

157.7740
157.7235
140.2526
136.2527
130.1760
129.1826
129.1471
128.5057
127.0837
125.4340
124.4535
124.2998
101.5357
61.3851
15.3777
N
N
O
O
9b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


9b
%Transmission
Wavenumber (cm-1)
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
4000
3500
3000
2500
2000
1500
1000
500
3051,99
2974,35
2917,14
2847,67
1703,52
1450,17
1397,05
1327,58
1094,67
1049,72
996,59
780,02
690,12


7.9245
7.9174
7.9007
7.8937
7.6873
7.6335
7.6255
7.6190
7.6103
7.6030
7.5973
7.5929
7.5582
7.5324
7.5251
7.5187
7.5120
7.5066
7.3991
7.3950
7.3920
7.3881
7.3728
7.3673
7.3621
6.4882
6.4346
6.4064
6.3832
6.3600
4.2958
4.2720
4.2482
4.2245
1.3519
1.3281
1.3045
CN
O
N
O
O
O
17a
1.00
0.98
2.07
1.03
0.98
1.01
1.00
1.02
2.04
3.11
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

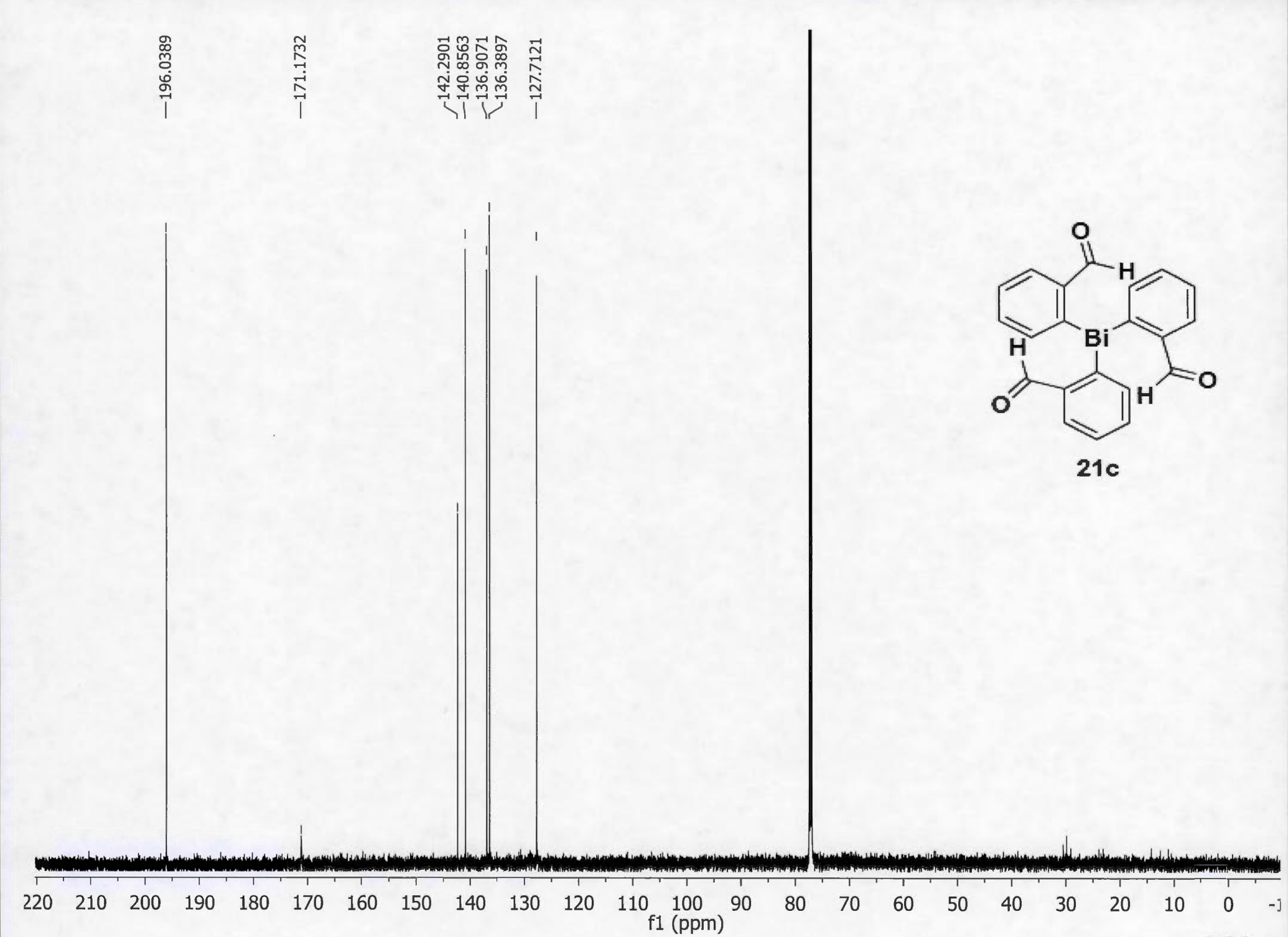

166.5060
159.2701
147.9677
142.8816
142.6100
140.1170
136.3760
130.2950
128.9727
127.7030
125.5597
120.5022
115.3137
107.0378
105.7704
60.8884
14.3938
CN
N
O
O
O
17a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


%Transmission
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
3079,85
2977,18
2923,94
2904,93
2227,90
1706,96
1661,96
1640,37
1541,57
1269,20
1181,15
17a

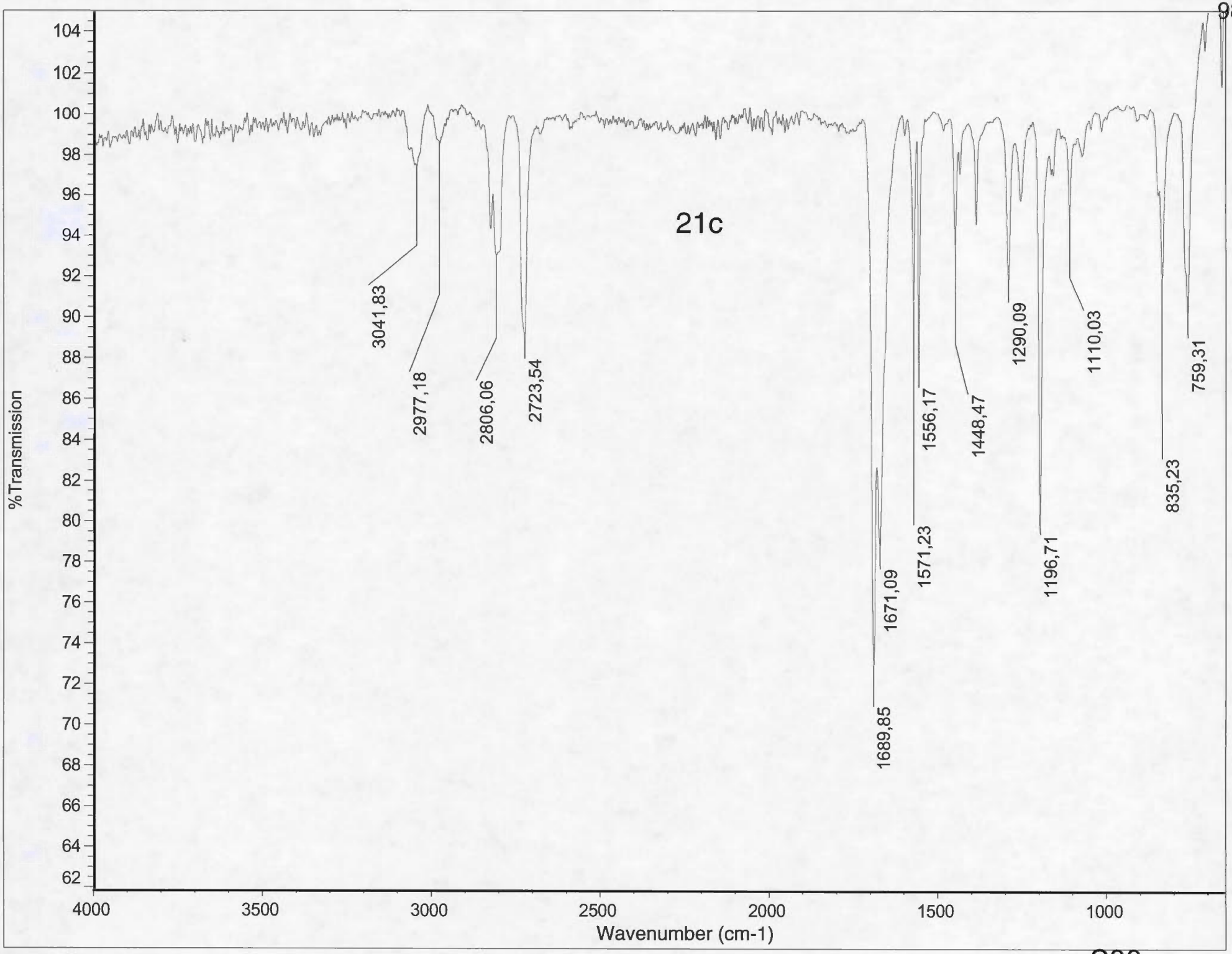

10.2273
8.0344
8.0094
7.5912
7.5660
7.5408
7.3633
7.3592
7.3384
7.3351
7.3145
7.3105
0.84
0.95
1.90
1.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

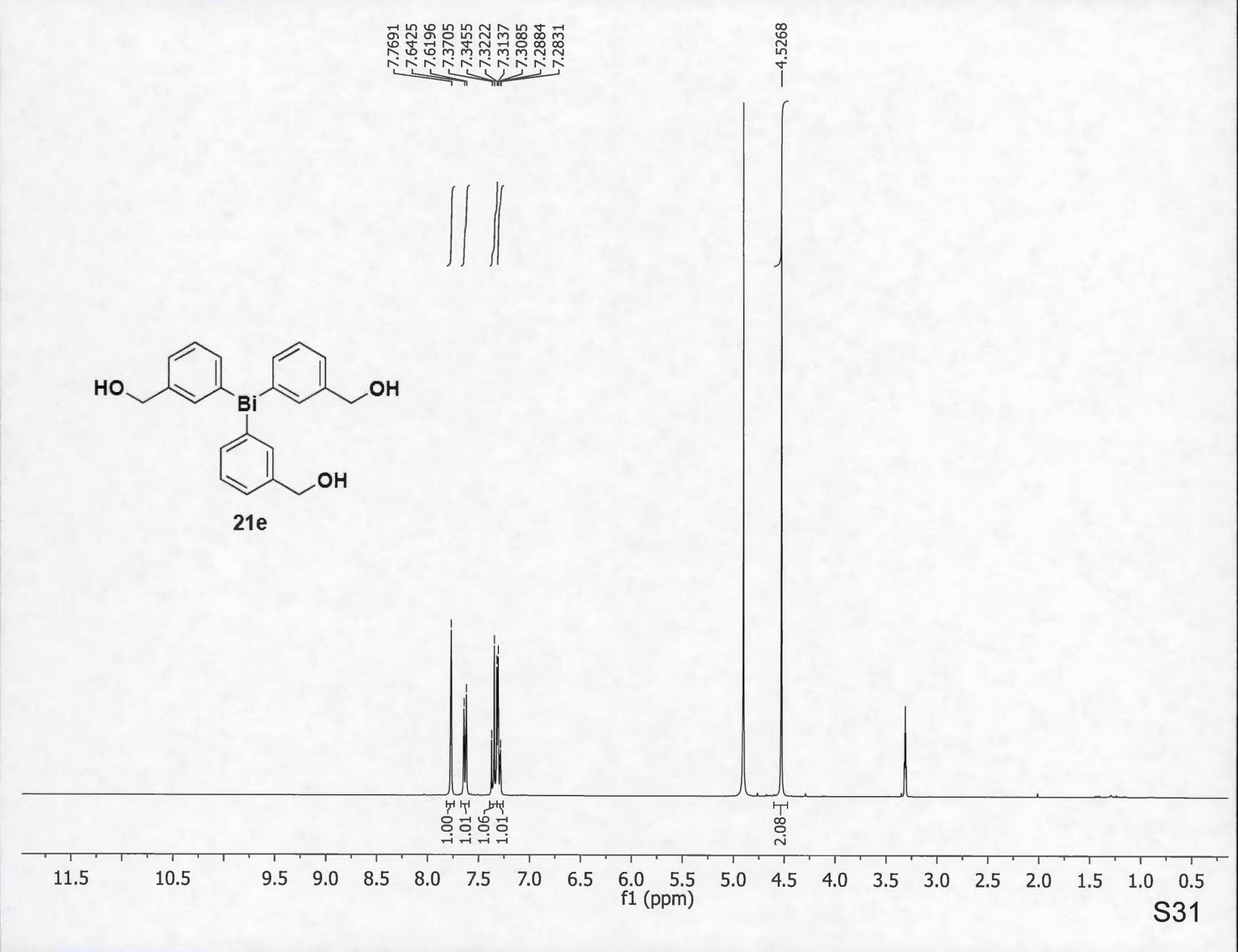
O
H
Bi
H
O
H
O

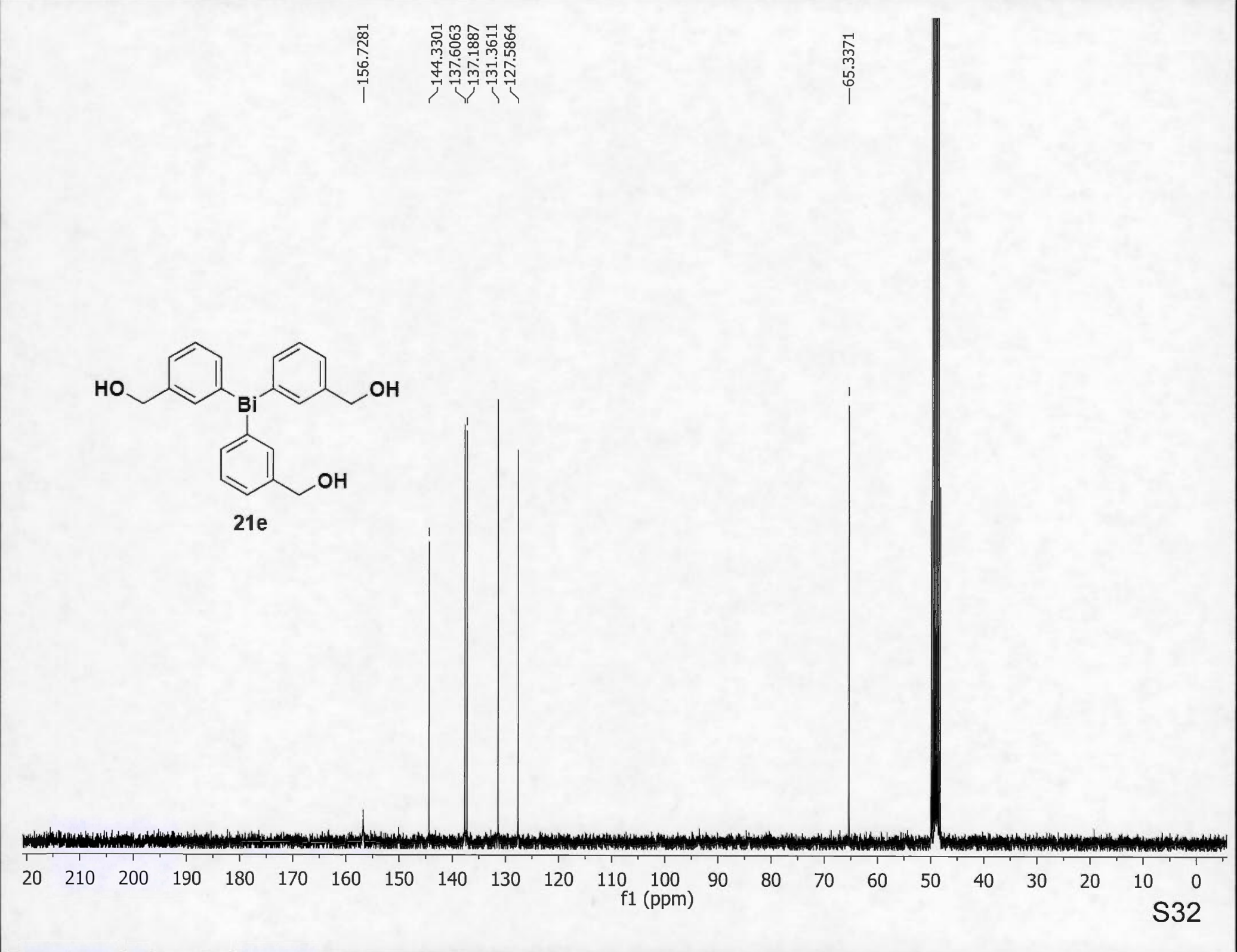
21c

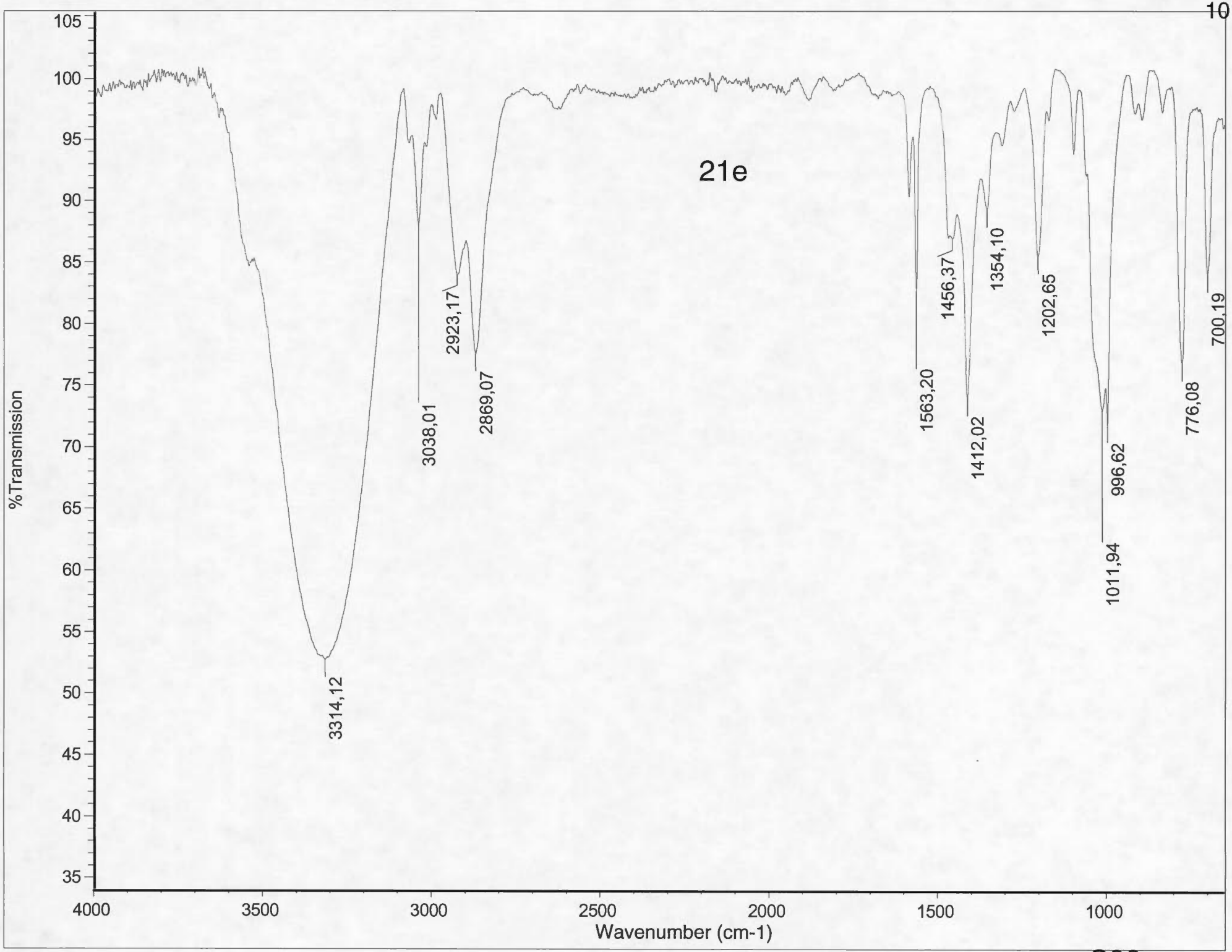

196.0389
171.1732
142.2901
140.8563
136.9071
136.3897
127.7121
O
H
Bi
H
O
O
H
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

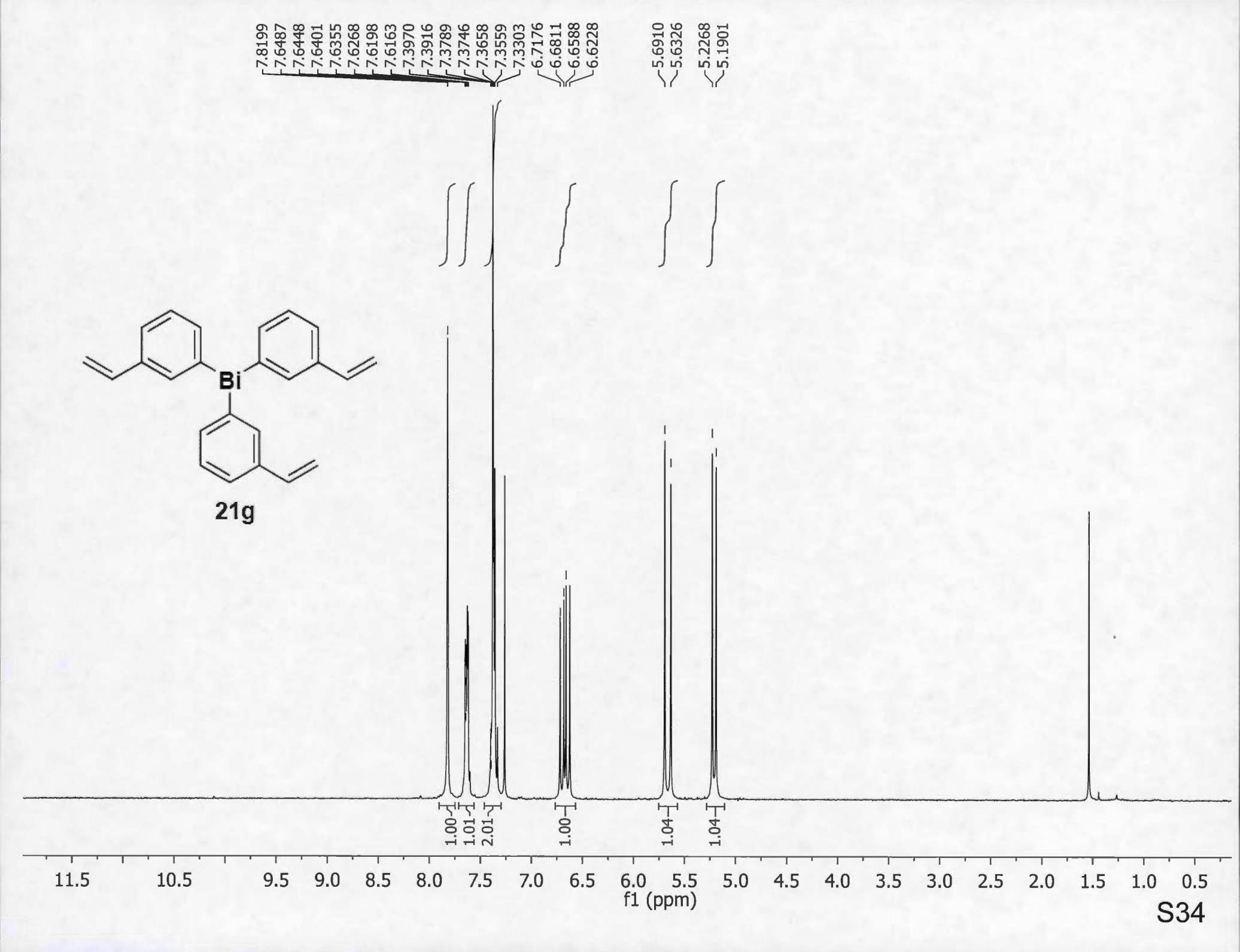
21c

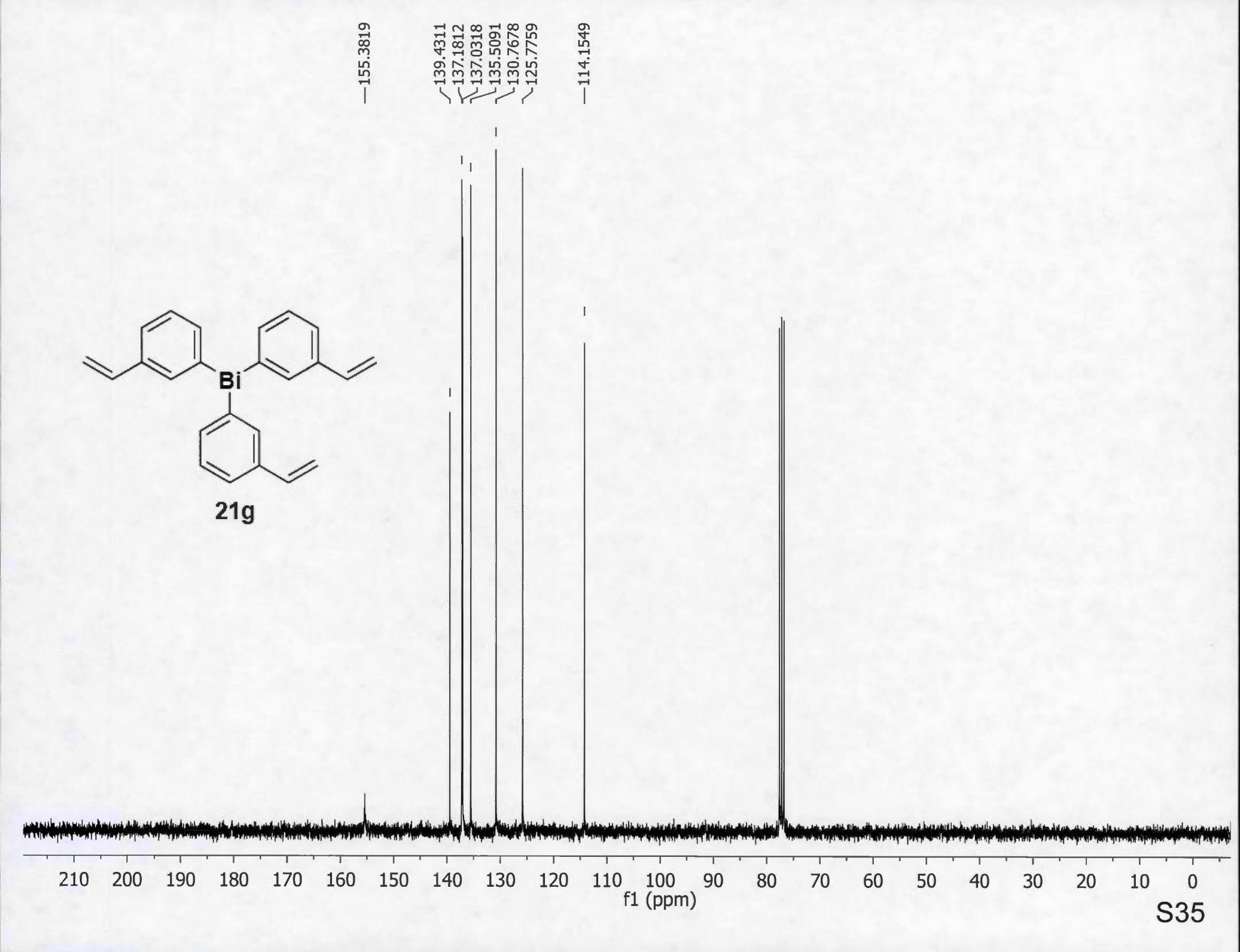

21c
%Transmission
Wavenumber (cm-1)
4000
3500
3000
2500
2000
1500
1000
104
102
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
3041,83
2977,18
2806,06
2723,54
1689,85
1671,09
1571,23
1556,17
1448,47
1290,09
1196,71
1110,03
835,23
759,31

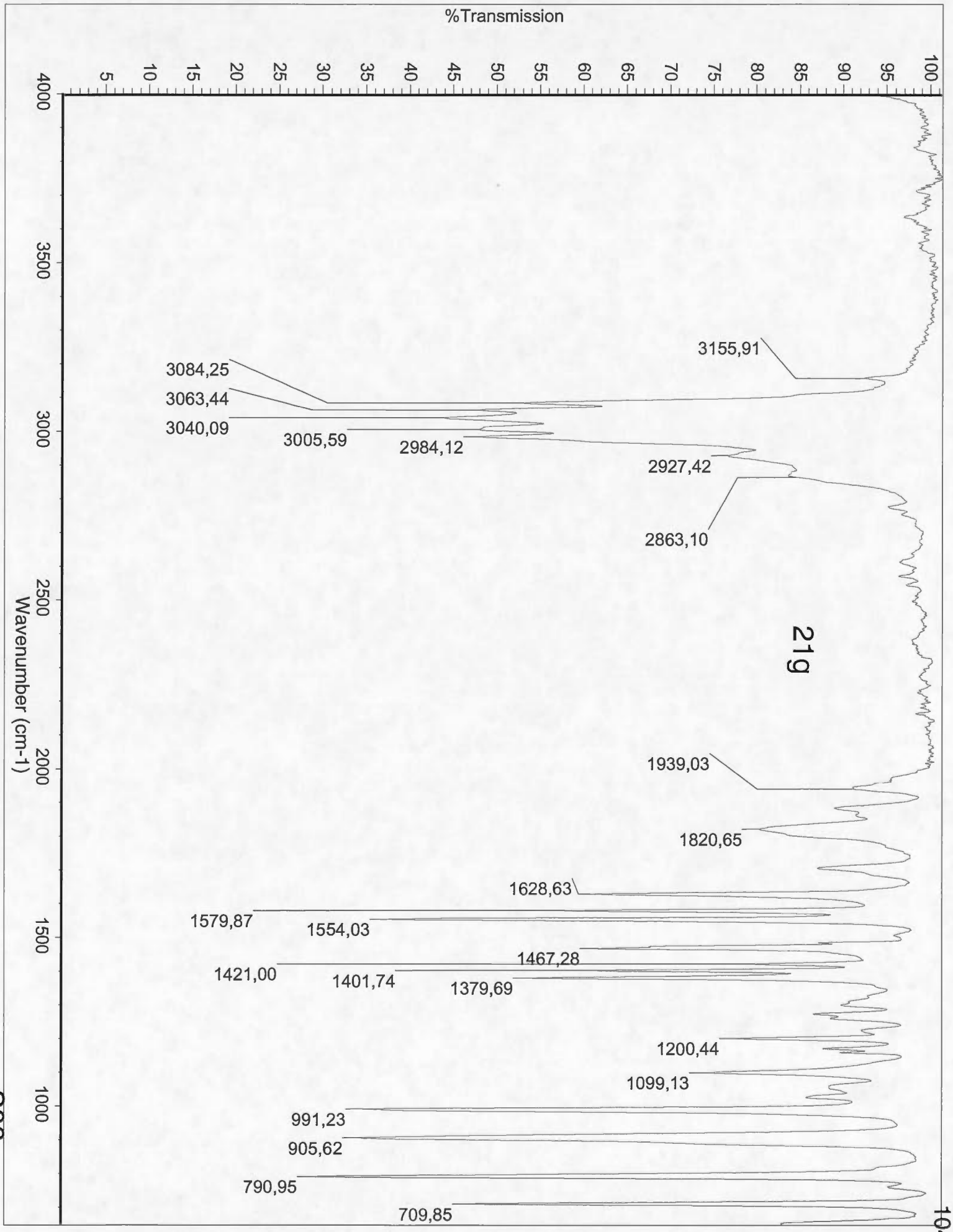

7.7691
7.6425
7.6196
7.3705
7.3455
7.3222
7.3137
7.3085
7.2884
7.2831
4.5268
HO
Bi
OH
OH
21e
1.00
1.01
1.06
1.01
2.08
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

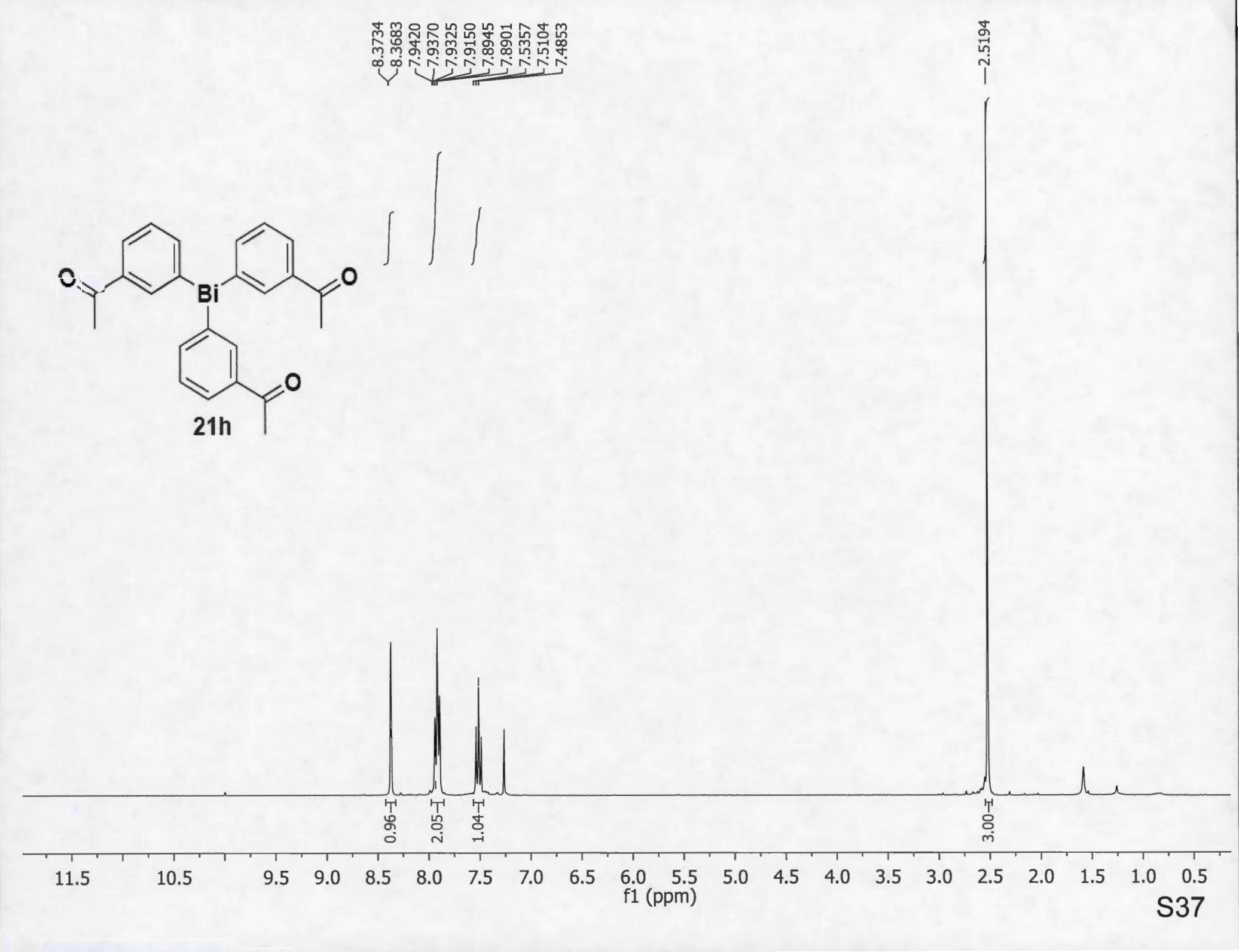

156.7281
144.3301
137.6063
137.1887
131.3611
127.5864
65.3371
HO
Bi
OH
OH
21e
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

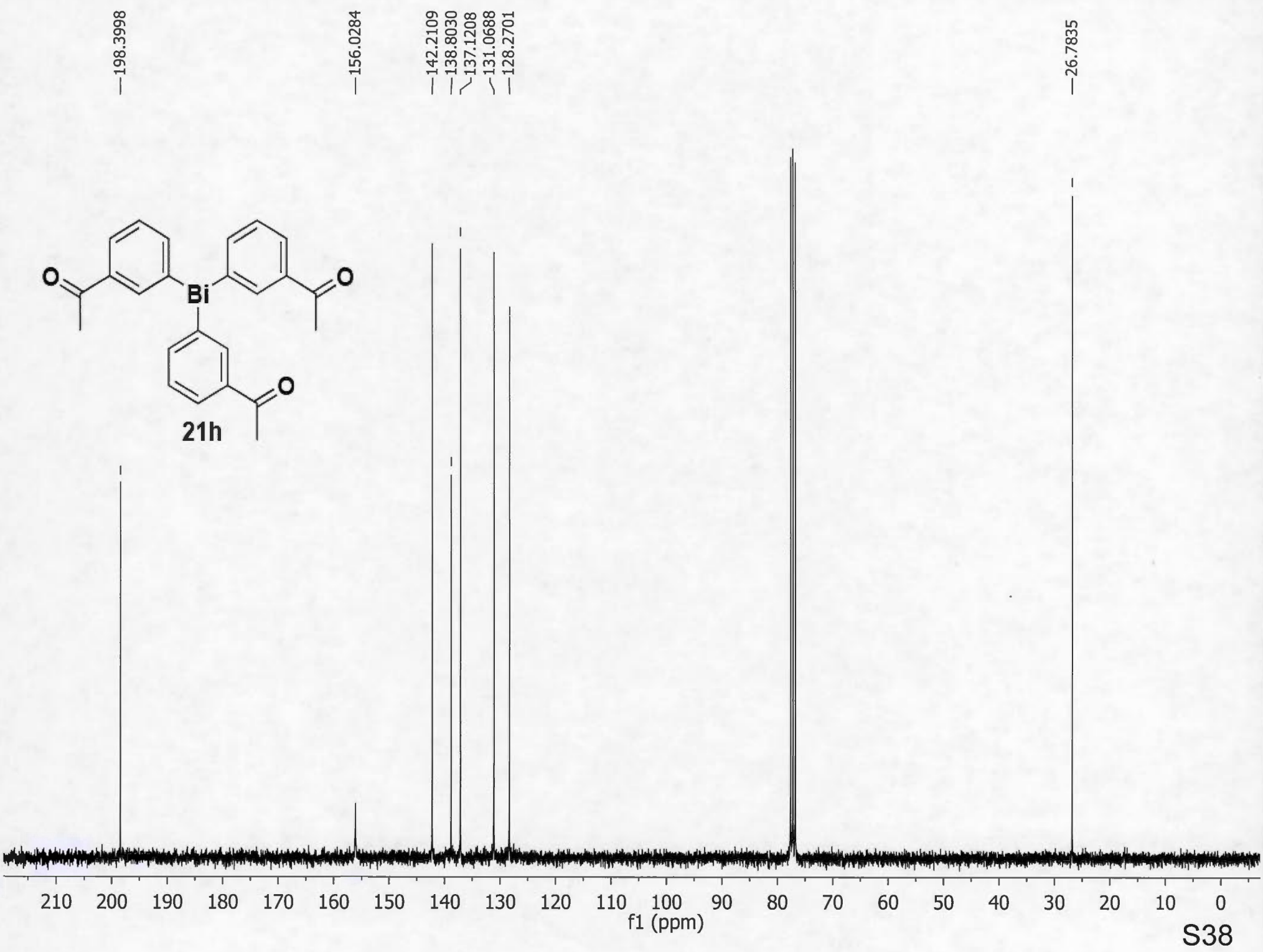

21e
%Transmission
Wavenumber (cm-1)
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
3314,12
3038,01
2923,17
2869,07
1563,20
1456,37
1412,02
1354,10
1202,65
1011,94
996,62
776,08
700,19


7.8199
7.6487
7.6448
7.6401
7.6355
7.6268
7.6198
7.6163
7.3970
7.3916
7.3789
7.3746
7.3658
7.3559
7.3303
6.7176
6.6811
6.6588
6.6228
5.6910
5.6326
5.2268
5.1901
Bi
21g
1.00
1.01
2.01
1.00
1.04
1.04
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

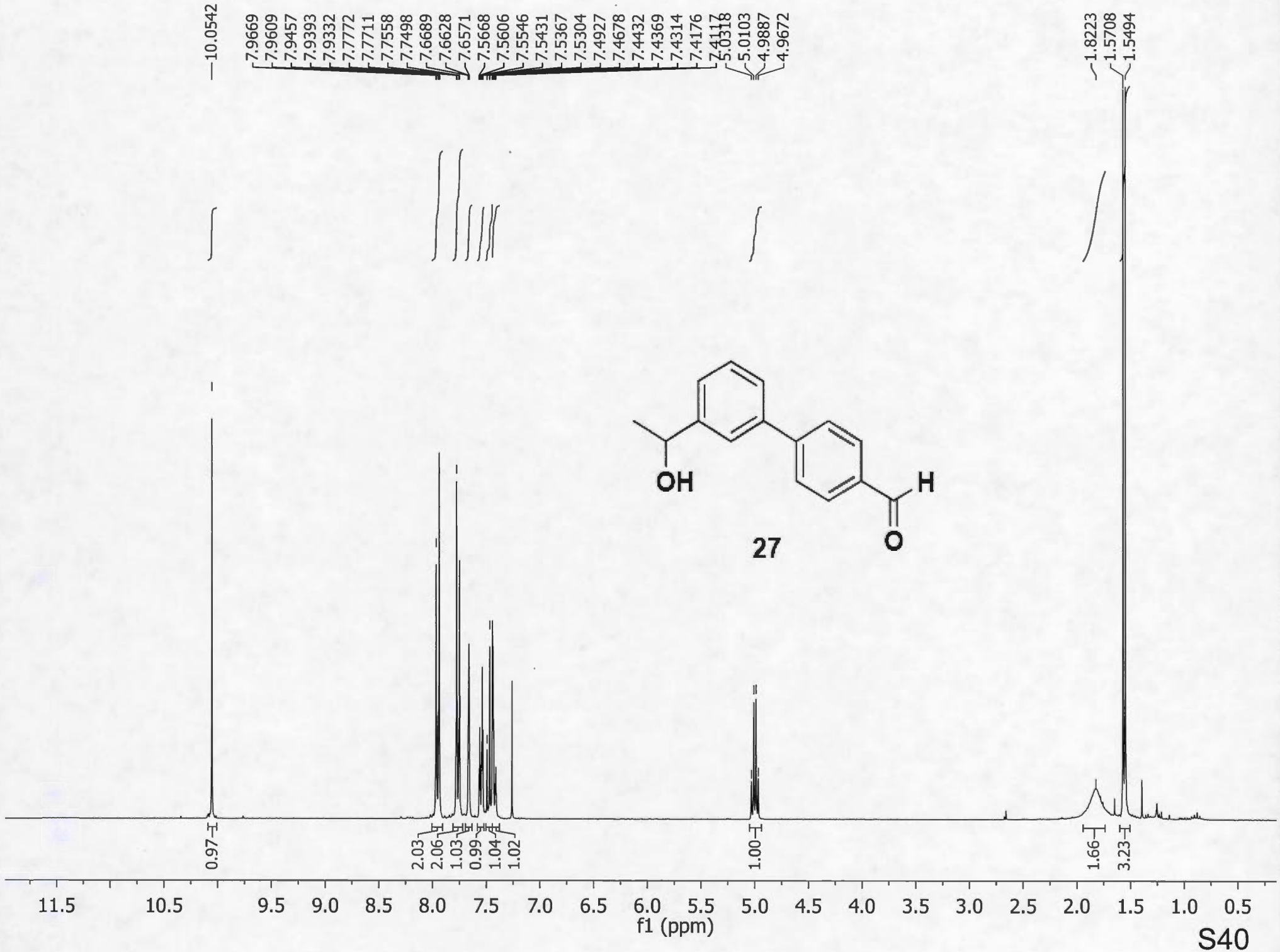

155.3819
139.4311
137.1812
137.0318
135.5091
130.7678
125.7759
114.1549
Bi
21g
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

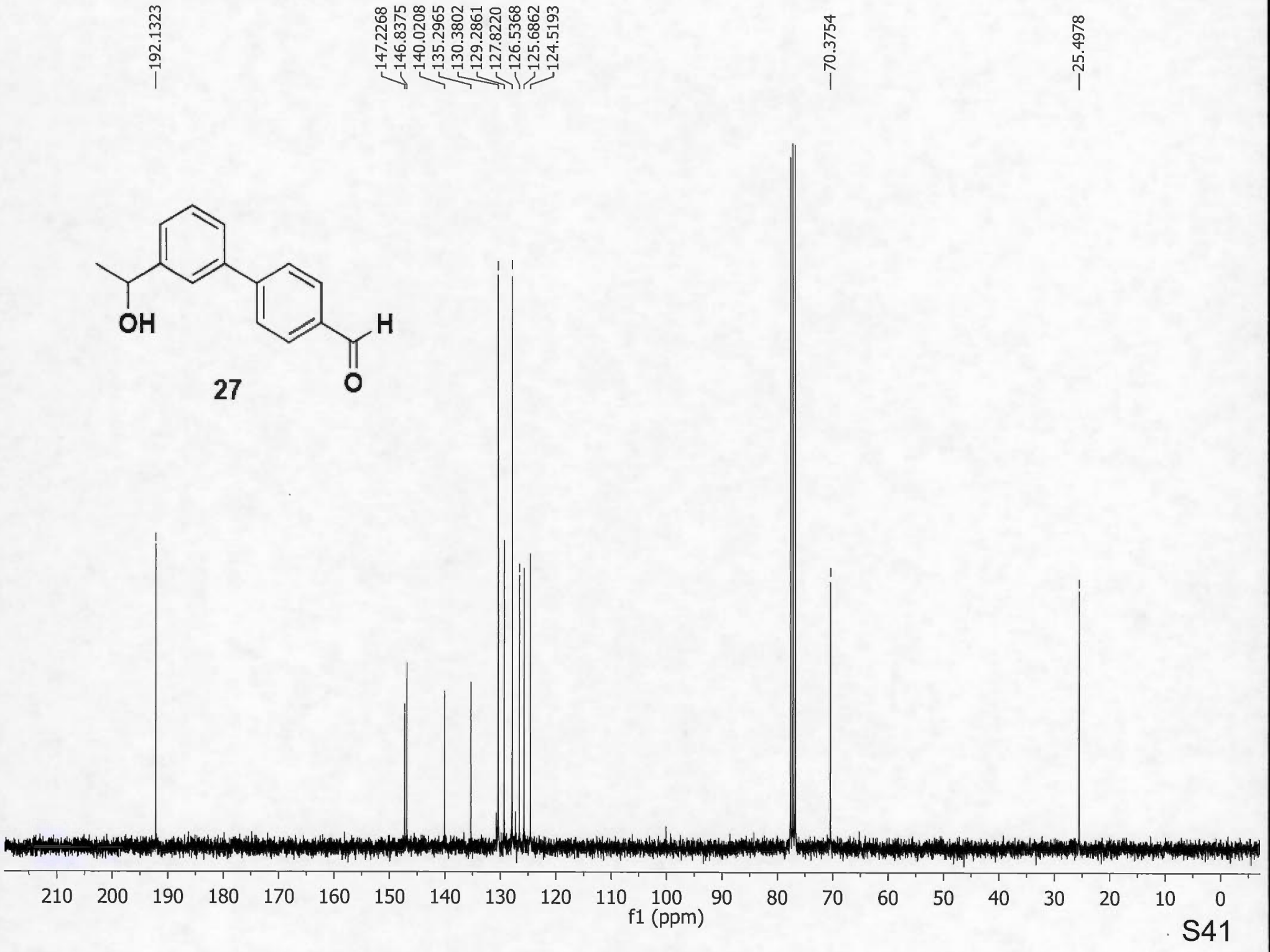

%Transmission
Wavenumber (cm-1)
3155,91
3084,25
3063,44
3040,09
3005,59
2984,12
2927,42
2863,10
1939,03
1820,65
1628,63
1579,87
1554,03
1467,28
1421,00
1401,74
1379,69
1200,44
1099,13
991,23
905,62
790,95
709,85
21g

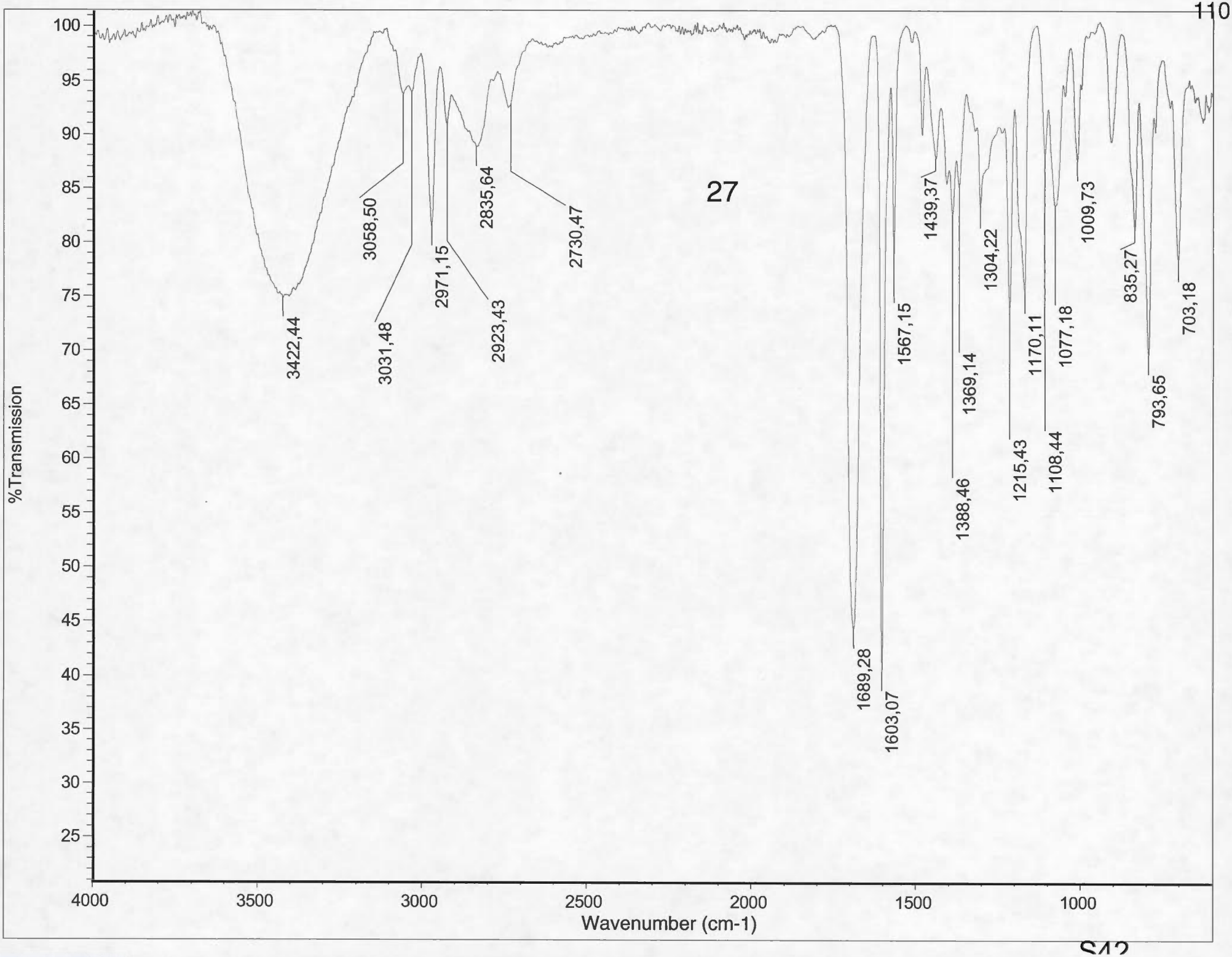

8.3734
8.3683
7.9420
7.9370
7.9325
7.9150
7.8945
7.8901
7.5357
7.5104
7.4853
2.5194
O
Bi
O
O
21h
0.96
2.05
1.04
3.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

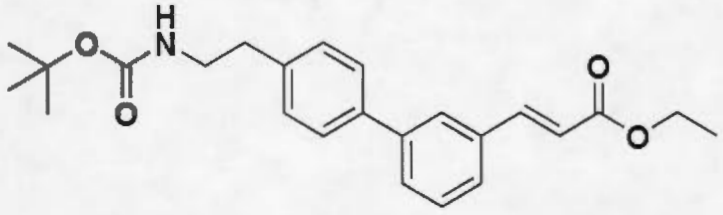

198.3998
156.0284
142.2109
138.8030
137.1208
131.0688
128.2701
26.7835
O
Bi
O
O
21h
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

%Transmission
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
3344,07
3050,78
3008,33
2923,43
21h
1678,16
1577,63
1559,39
1404,22
1355,73
1276,25
1254,70
947,56
788,49
691,00

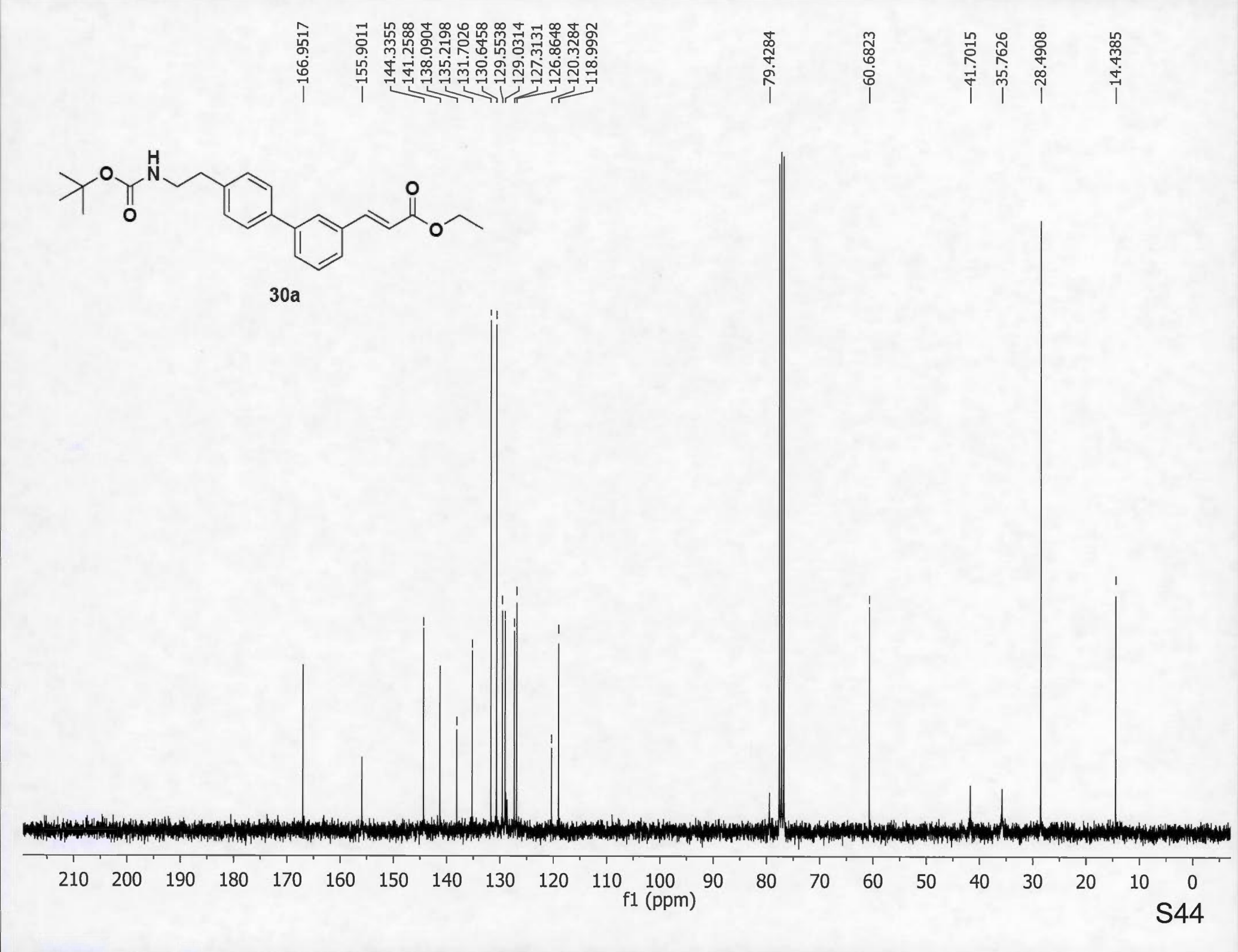

10.0542
7.9669
7.9609
7.9457
7.9393
7.9332
7.7772
7.7711
7.7558
7.7498
7.6689
7.6628
7.6571
7.5668
7.5606
7.5546
7.5431
7.5367
7.5304
7.4927
7.4678
7.4432
7.4369
7.4314
7.4176
7.4117
5.0318
5.0103
4.9887
4.9672
1.8223
1.5708
1.5494
OH
H
O
27
0.97
2.03
2.06
1.03
0.99
1.04
1.02
1.00
1.66
3.23
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

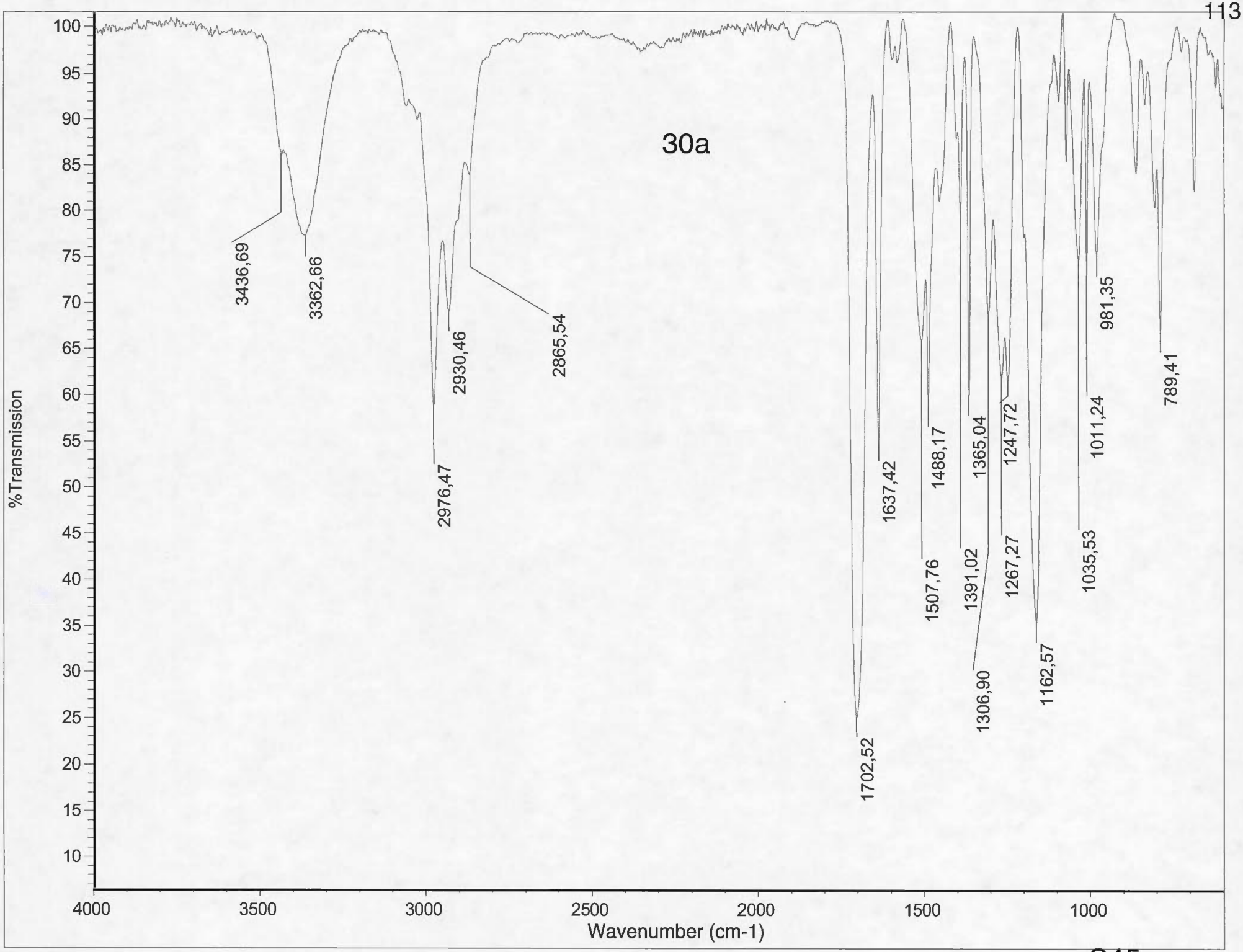

192.1323
147.2268
146.8375
140.0208
135.2965
130.3802
129.2861
127.8220
126.5368
125.6862
124.5193
70.3754
25.4978
OH
H
O
27
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

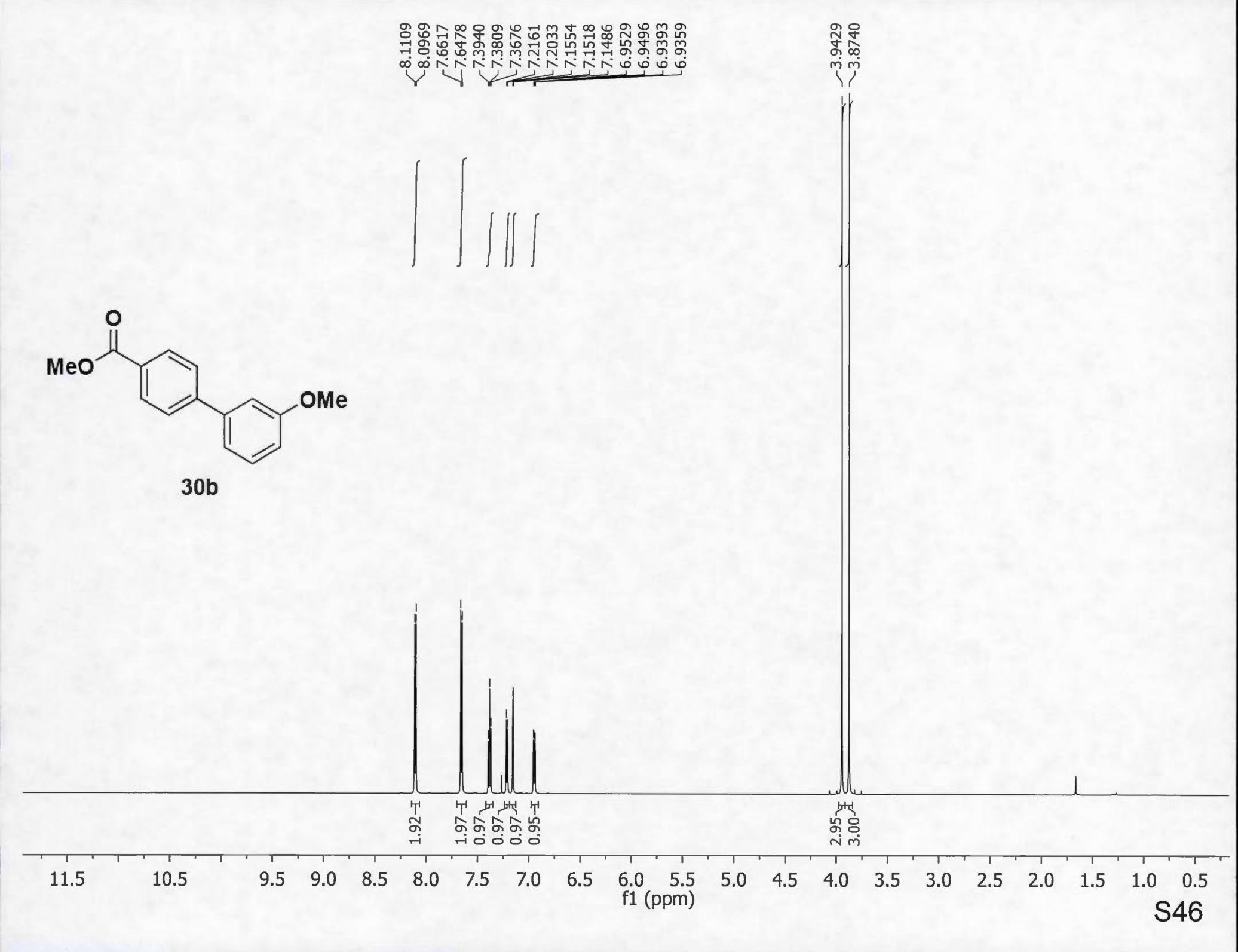

27
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
4000
3500
3000
2500
2000
1500
1000
3422,44
3058,50
3031,48
2971,15
2923,43
2835,64
2730,47
1689,28
1603,07
1567,15
1439,37
1388,46
1369,14
1304,22
1215,43
1170,11
1108,44
1077,18
1009,73
835,27
793,65
703,18

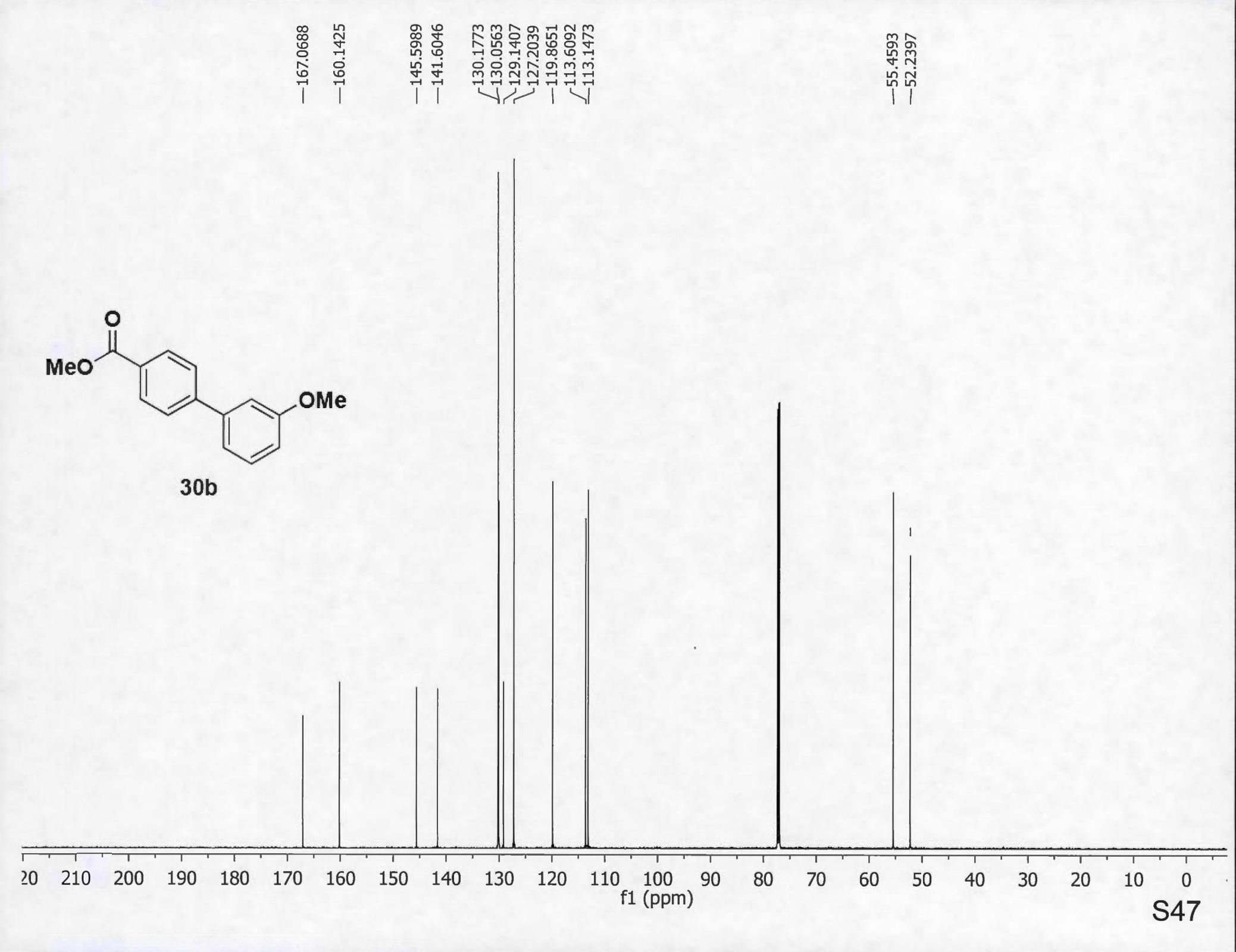


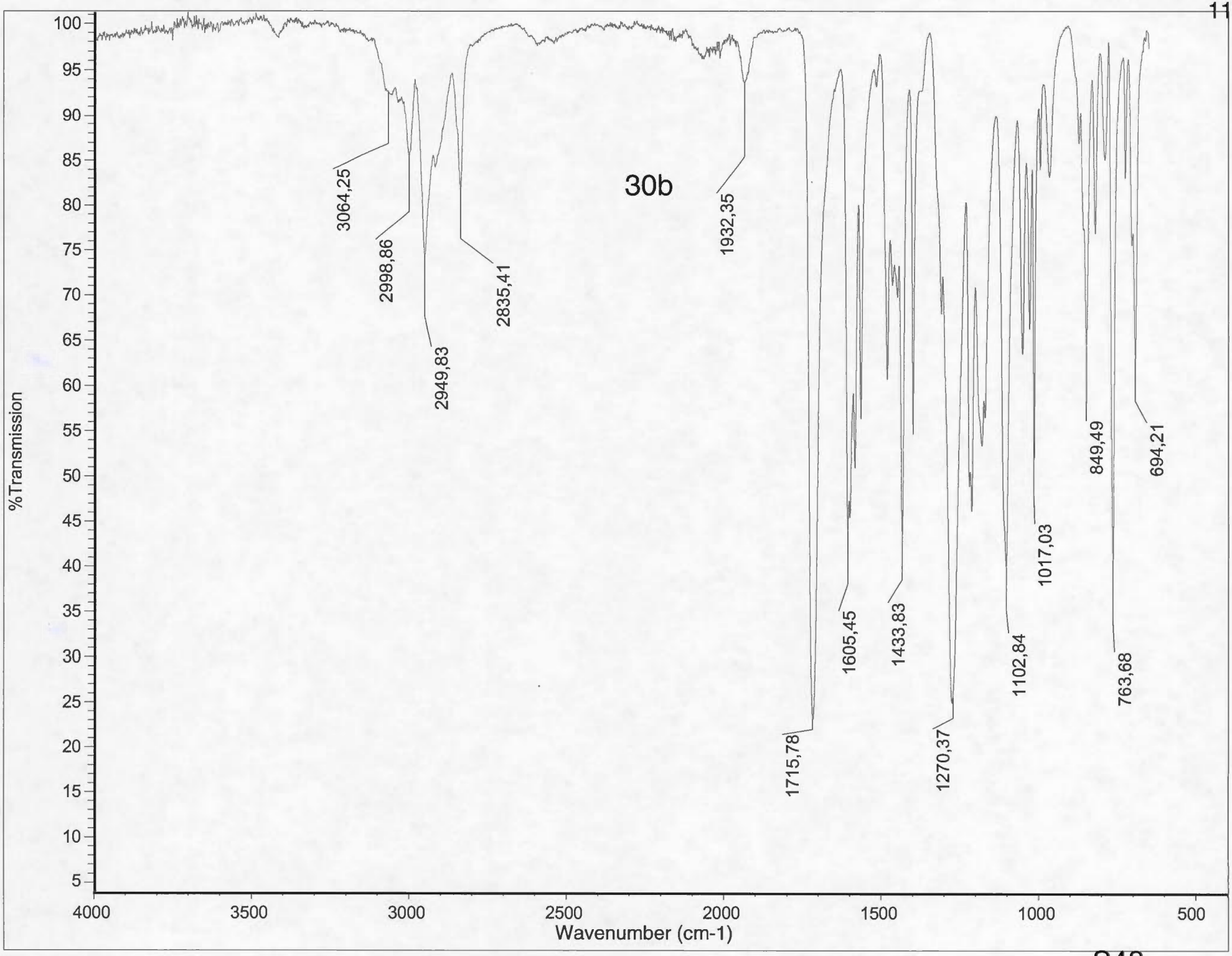
30a

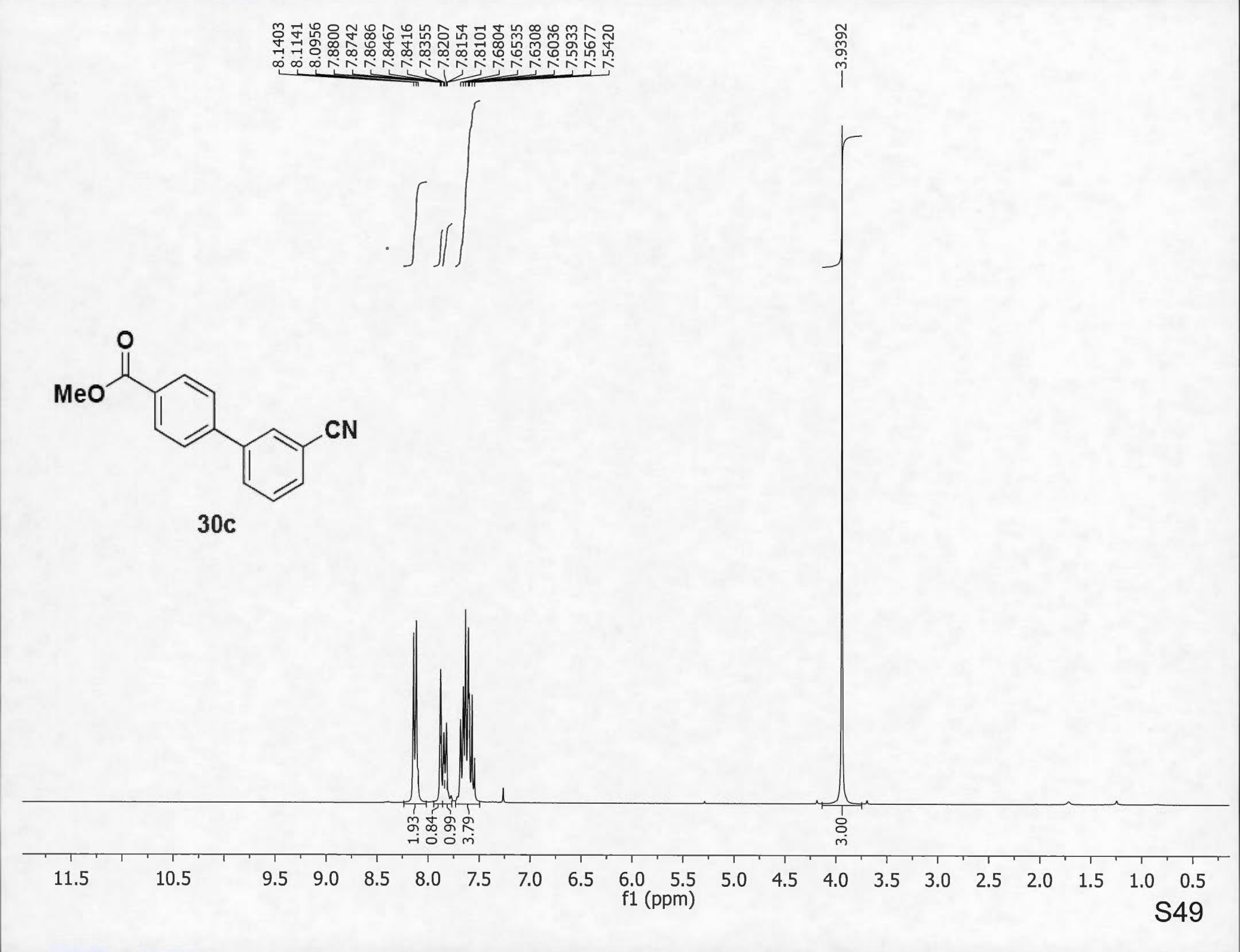

166.9517
155.9011
144.3355
141.2588
138.0904
135.2198
131.7026
130.6458
129.5538
129.0314
127.3131
126.8648
120.3284
118.9992
79.4284
60.6823
41.7015
35.7626
28.4908
14.4385
30a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

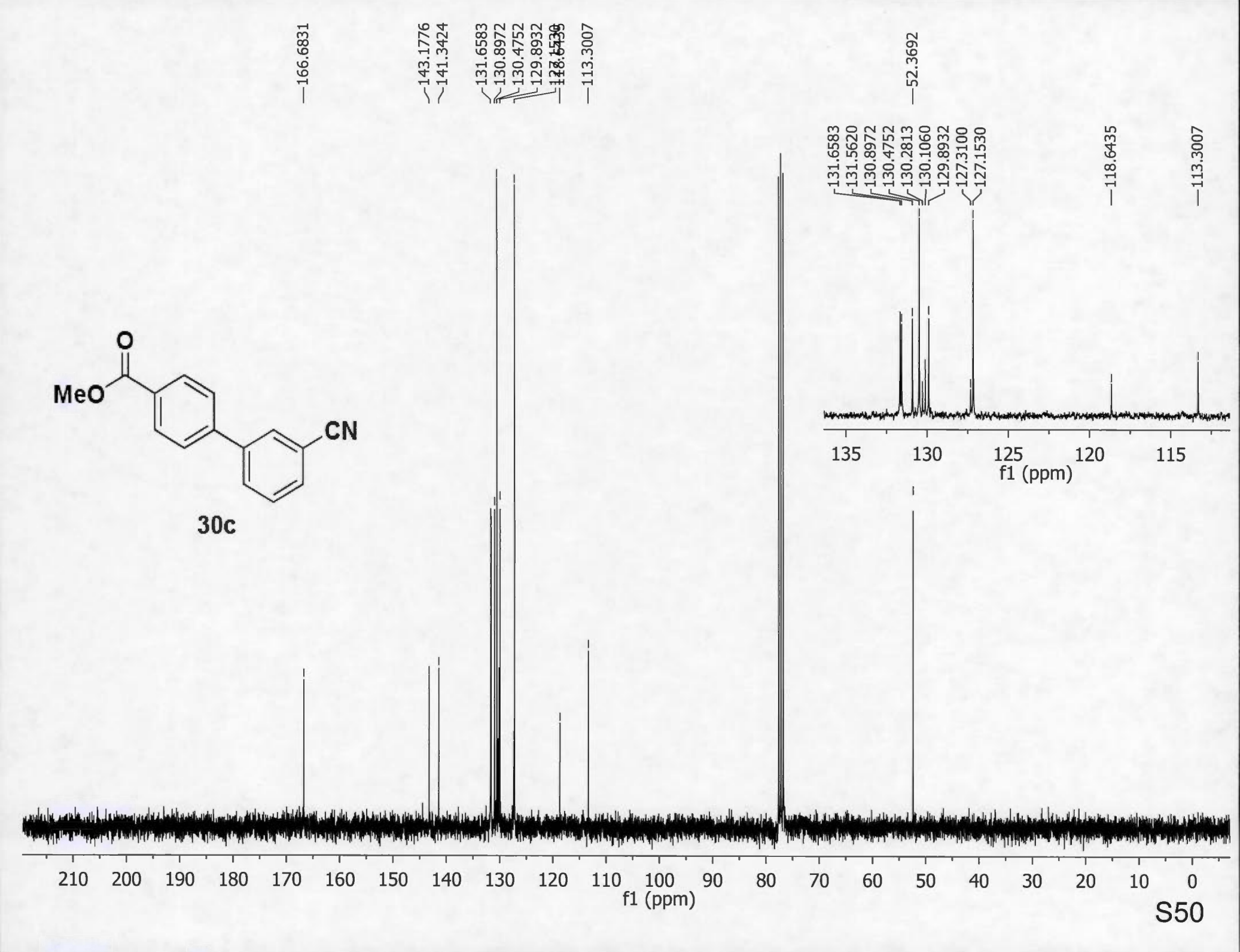

30a
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4000
3500
3000
2500
2000
1500
1000
3436,69
3362,66
2976,47
2930,46
2865,54
1702,52
1637,42
1507,76
1488,17
1391,02
1365,04
1306,90
1267,27
1247,72
1162,57
1035,53
1011,24
981,35
789,41

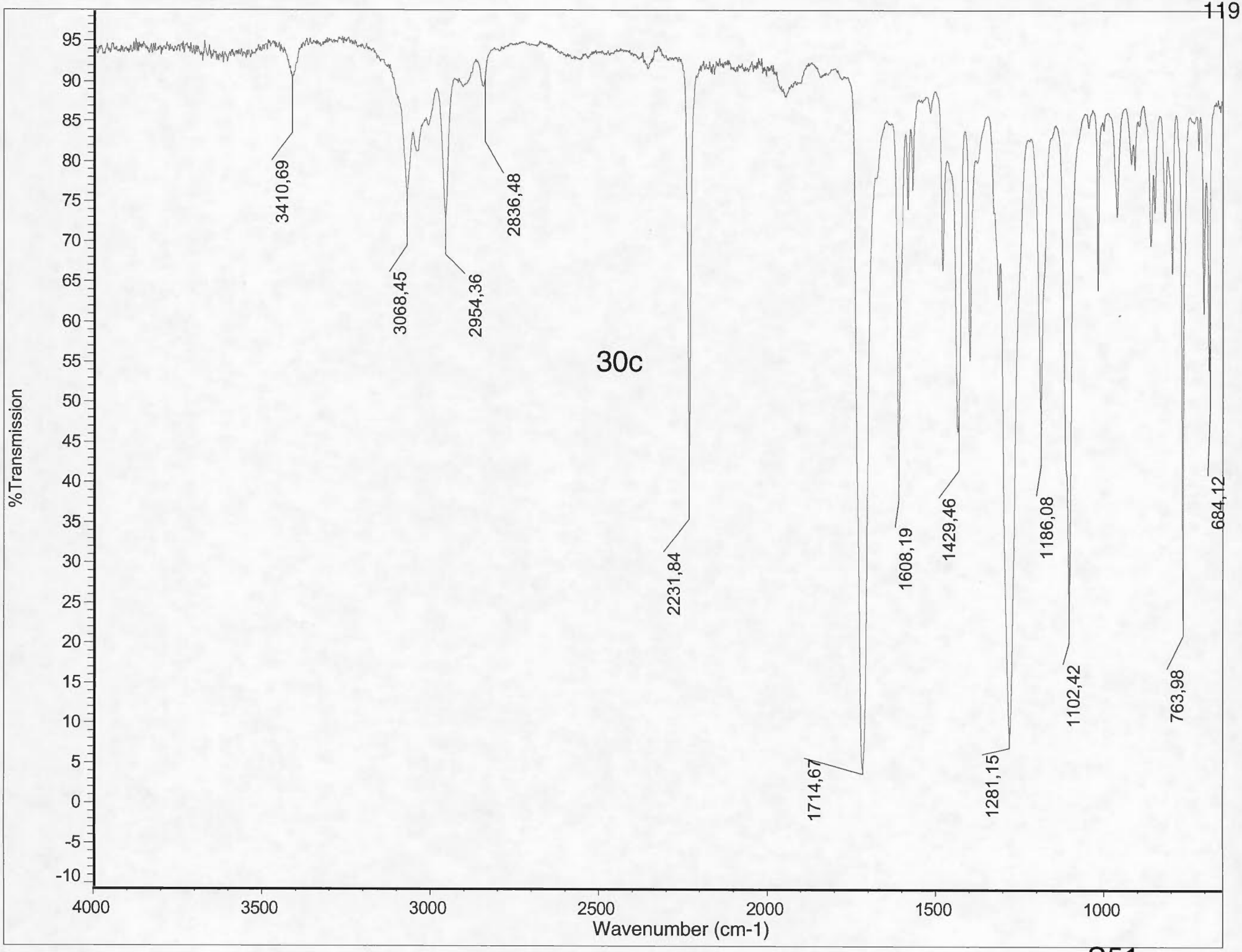

8.1109
8.0969
7.6617
7.6478
7.3940
7.3809
7.3676
7.2161
7.2033
7.1554
7.1518
7.1486
6.9529
6.9496
6.9393
6.9359
3.9429
3.8740
MeO
O
OMe
30b
1.92
1.97
0.97
0.97
0.97
0.95
2.95
3.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

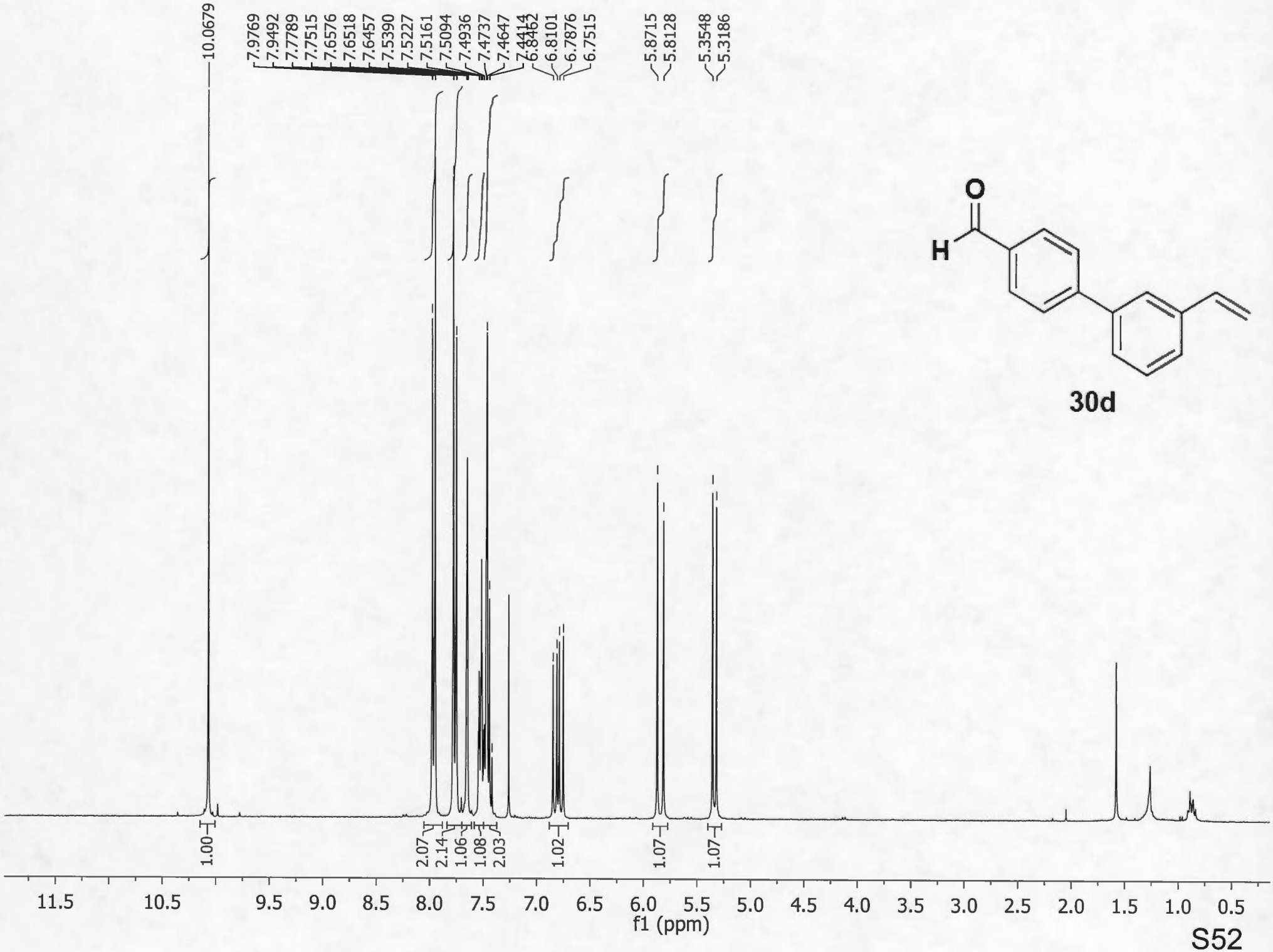

167.0688
160.1425
145.5989
141.6046
130.1773
130.0563
129.1407
127.2039
119.8651
113.6092
113.1473
55.4593
52.2397
MeO
O
OMe
30b
f1 (ppm)


30b
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
4000
3500
3000
2500
2000
1500
1000
500
3064,25
2998,86
2949,83
2835,41
1932,35
1715,78
1605,45
1433,83
1270,37
1102,84
1017,03
849,49
763,68
694,21


8.1403
8.1141
8.0956
7.8800
7.8742
7.8686
7.8467
7.8416
7.8355
7.8207
7.8154
7.8101
7.6804
7.6535
7.6308
7.6036
7.5933
7.5677
7.5420
3.9392
O
MeO
CN
30c
1.93
0.84
0.99
3.79
3.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


166.6831
143.1776
141.3424
131.6583
130.8972
130.4752
129.8932
113.3007
52.3692
131.6583
131.5620
130.8972
130.4752
130.2813
130.1060
129.8932
127.3100
127.1530
118.6435
113.3007
135
130
125
120
115
f1 (ppm)
MeO
O
CN
30c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

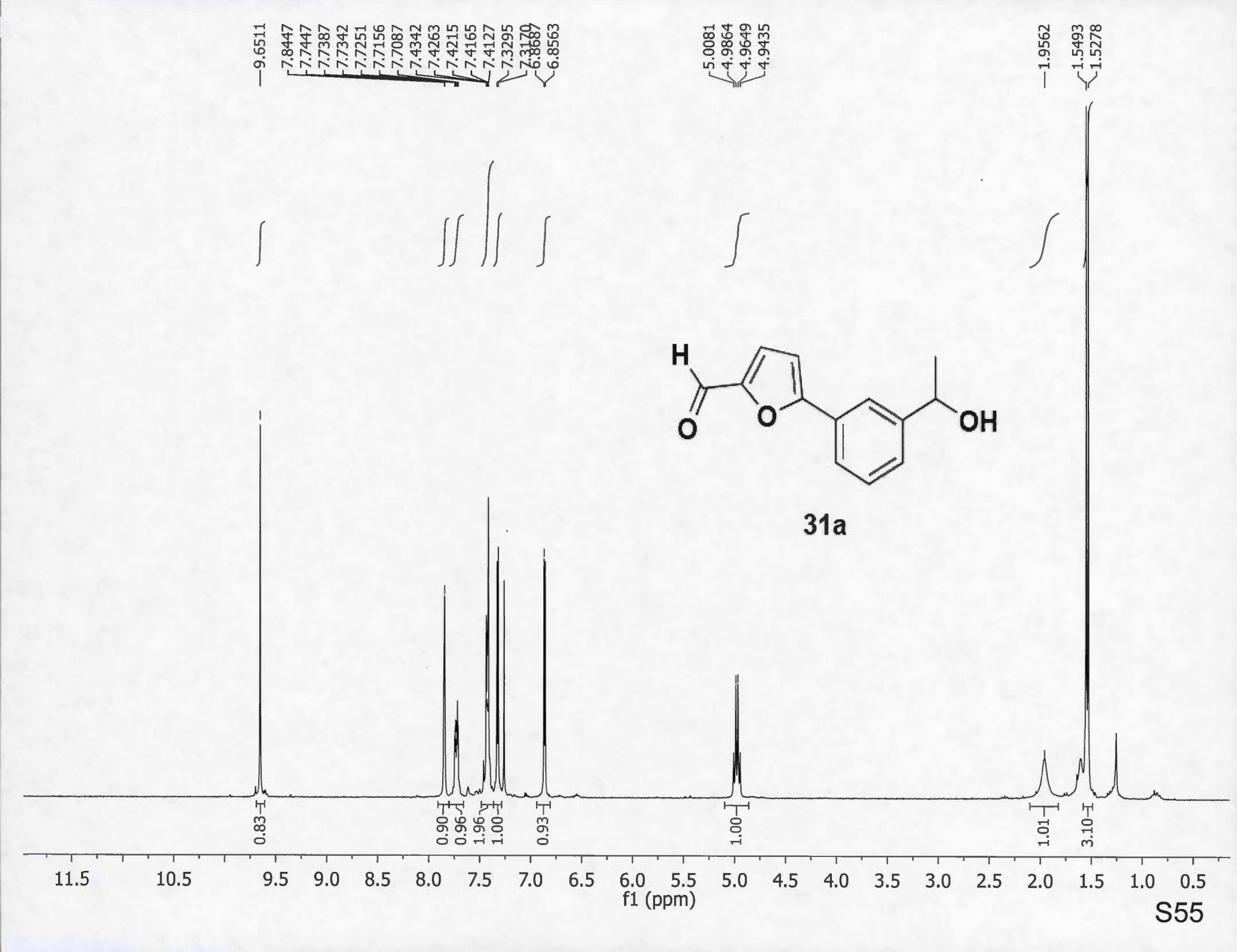

30c
%Transmission
Wavenumber (cm-1)
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
4000
3500
3000
2500
2000
1500
1000
3410,69
3068,45
2954,36
2836,48
2231,84
1714,67
1608,19
1429,46
1281,15
1186,08
1102,42
763,98
684,12

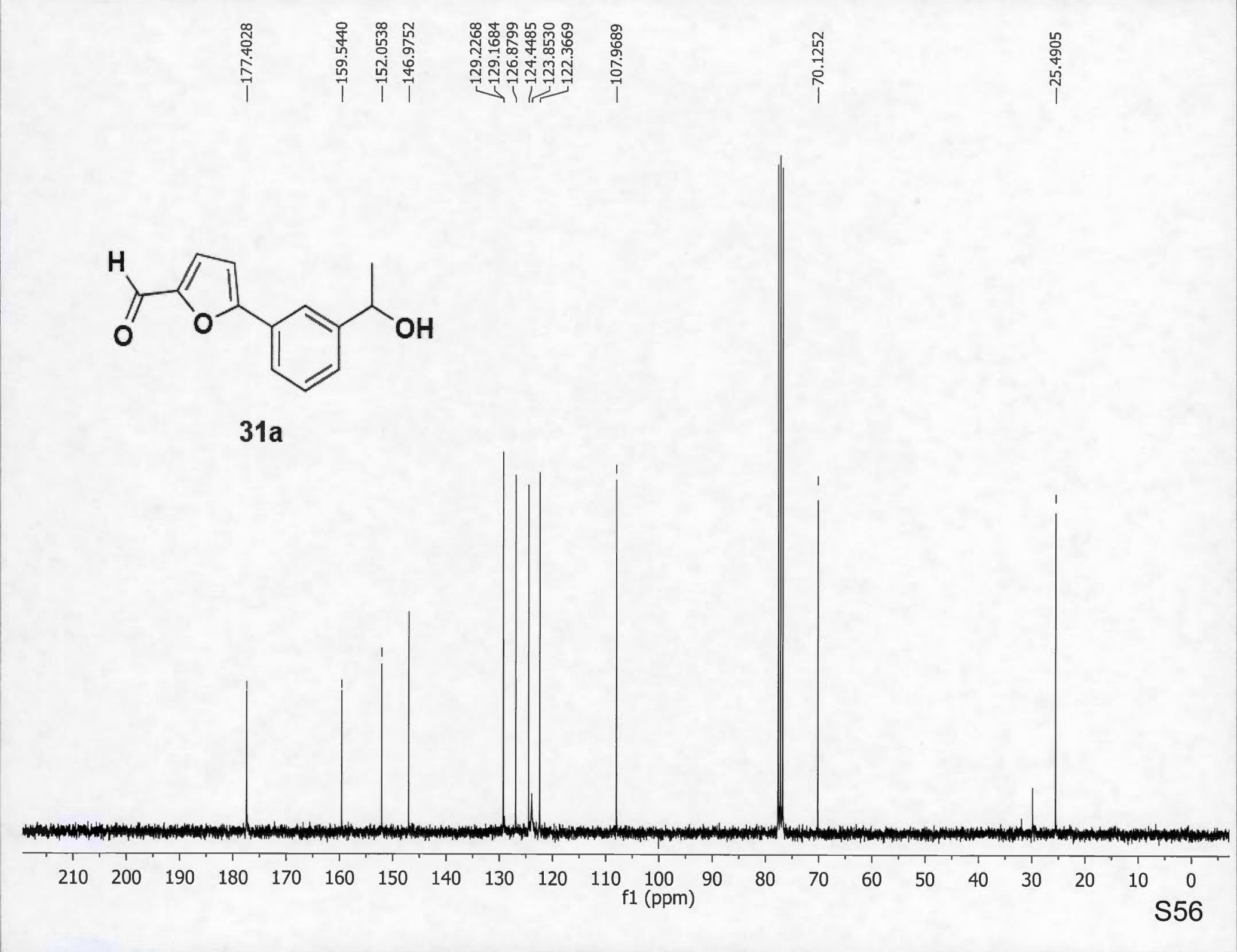

10.0679
7.9769
7.9492
7.7789
7.7515
7.6576
7.6518
7.6457
7.5390
7.5227
7.5161
7.5094
7.4936
7.4737
7.4647
7.4414
7.4362
6.8101
6.7876
6.7515
5.8715
5.8128
5.3548
5.3186
1.00
2.07
2.14
1.06
1.08
2.03
1.02
1.07
1.07
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
O
H
30d

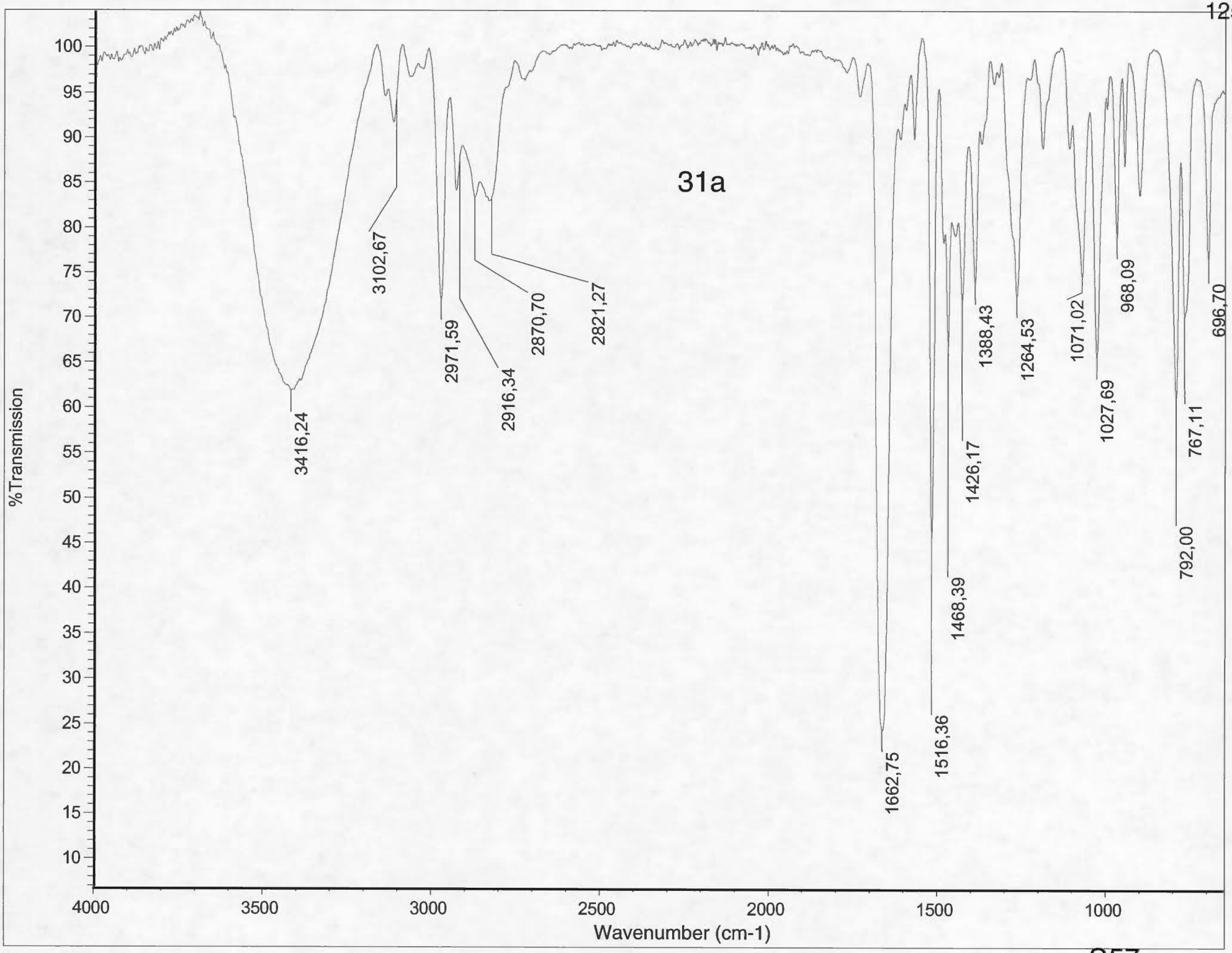
192.0347
147.2060
138.4634
136.5877
130.3920
129.3381
127.8566
126.9308
126.3060
125.4712
114.8736
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
H
O

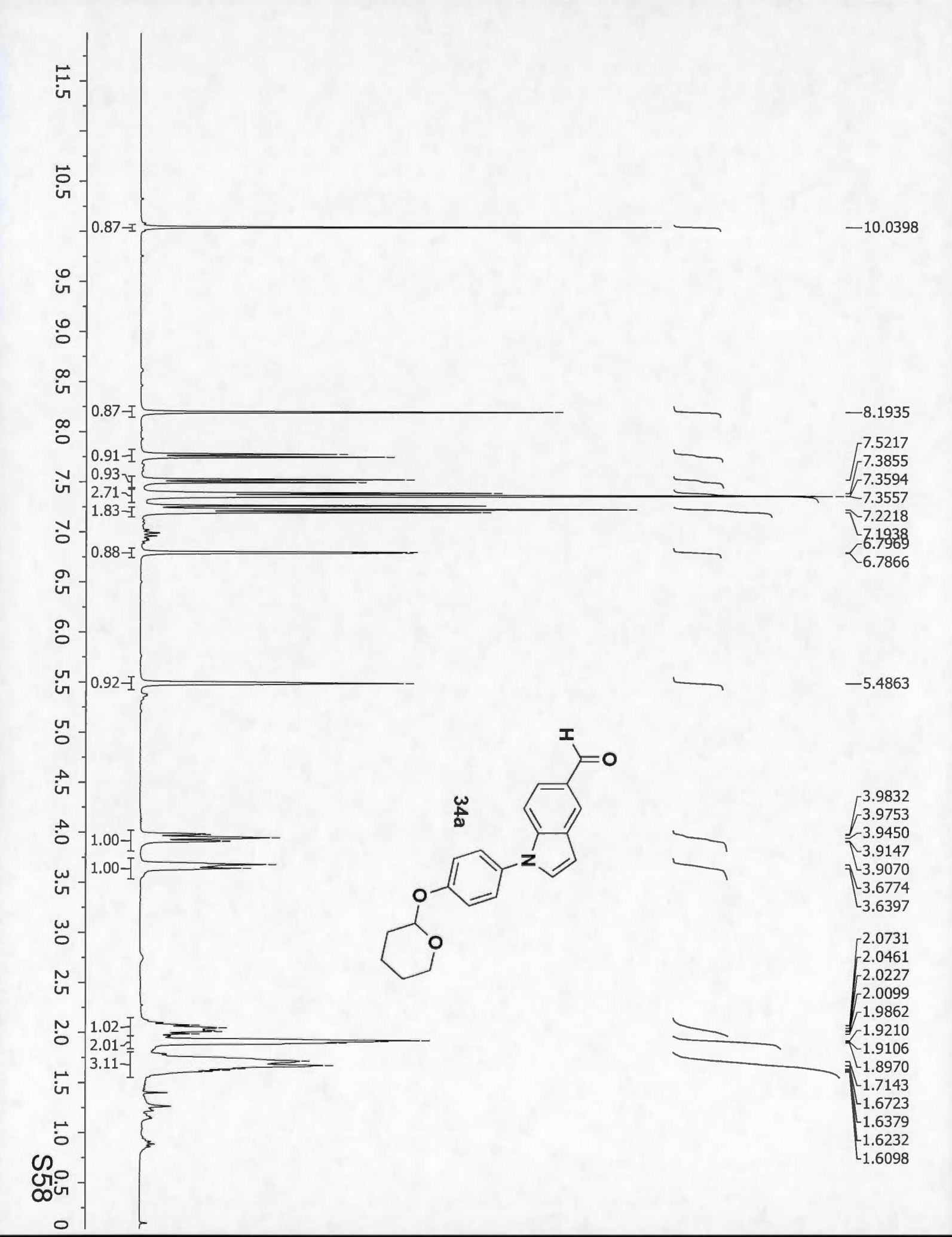
30d

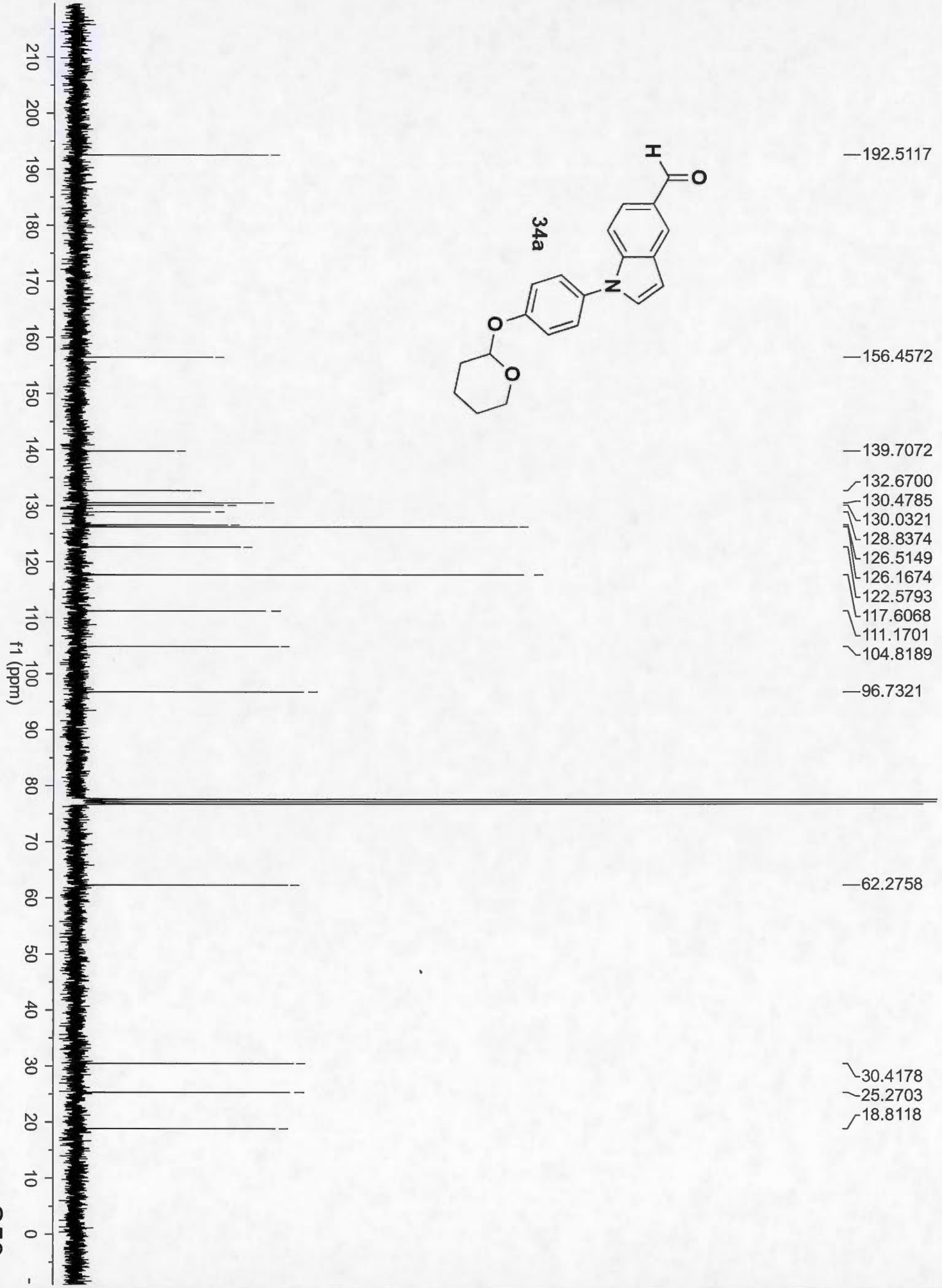
%Transmission
52
54
56
58
60
62
64
66
68
70
72
74
76
78
80
82
84
86
88
90
92
94
96
98
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
3406,89
3057,04
2916,34
2844,08
2733,80
1691,85
1600,58
1383,83
1208,90
1167,07
988,34
836,23
790,60
699,33
30d

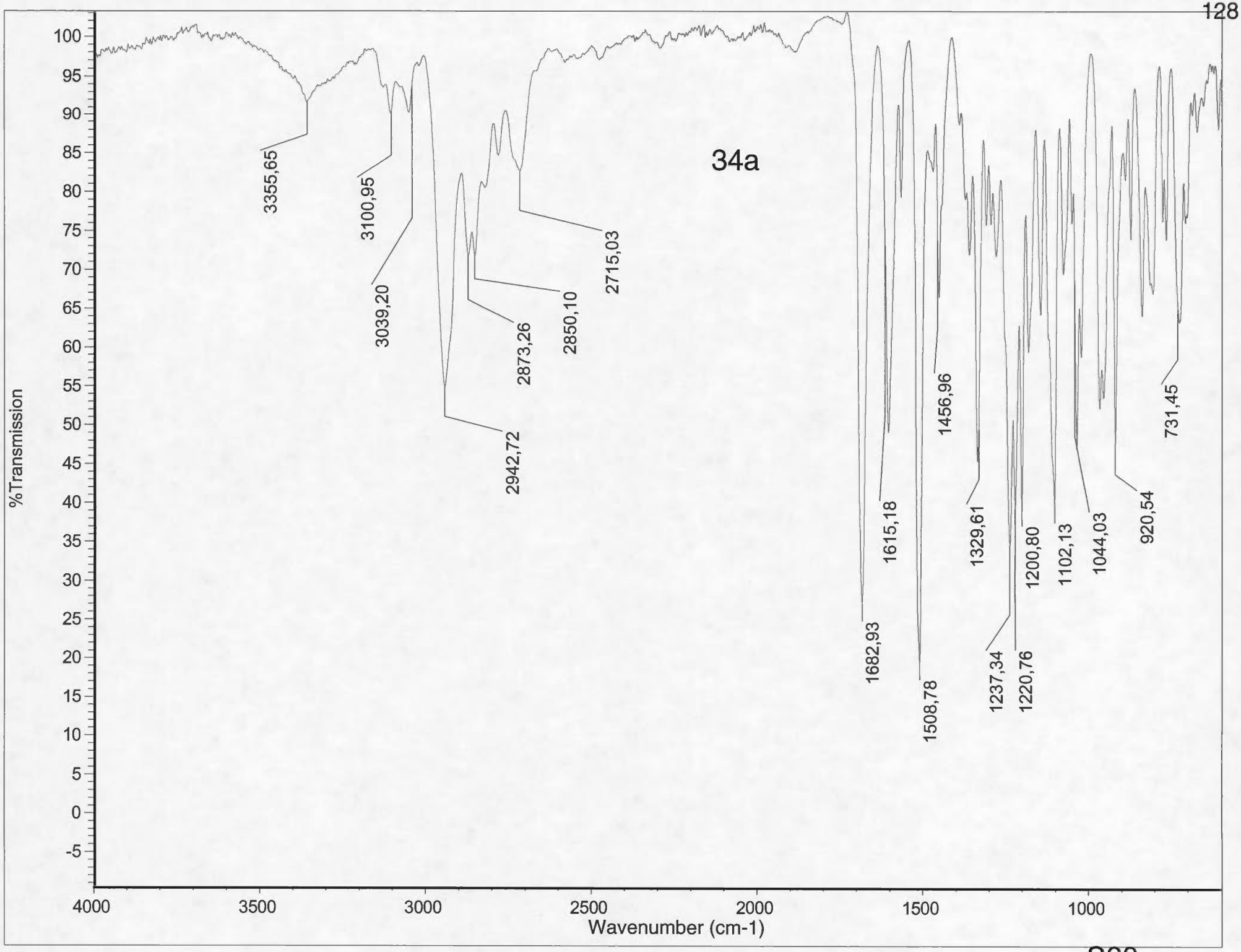

9.6511
7.8447
7.7447
7.7387
7.7342
7.7251
7.7156
7.7087
7.4342
7.4263
7.4215
7.4165
7.4127
7.3295
7.3170
6.8687
6.8563
5.0081
4.9864
4.9649
4.9435
1.9562
1.5493
1.5278
H
O
O
OH
31a
0.83
0.90
0.96
1.96
1.00
0.93
1.00
1.01
3.10
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

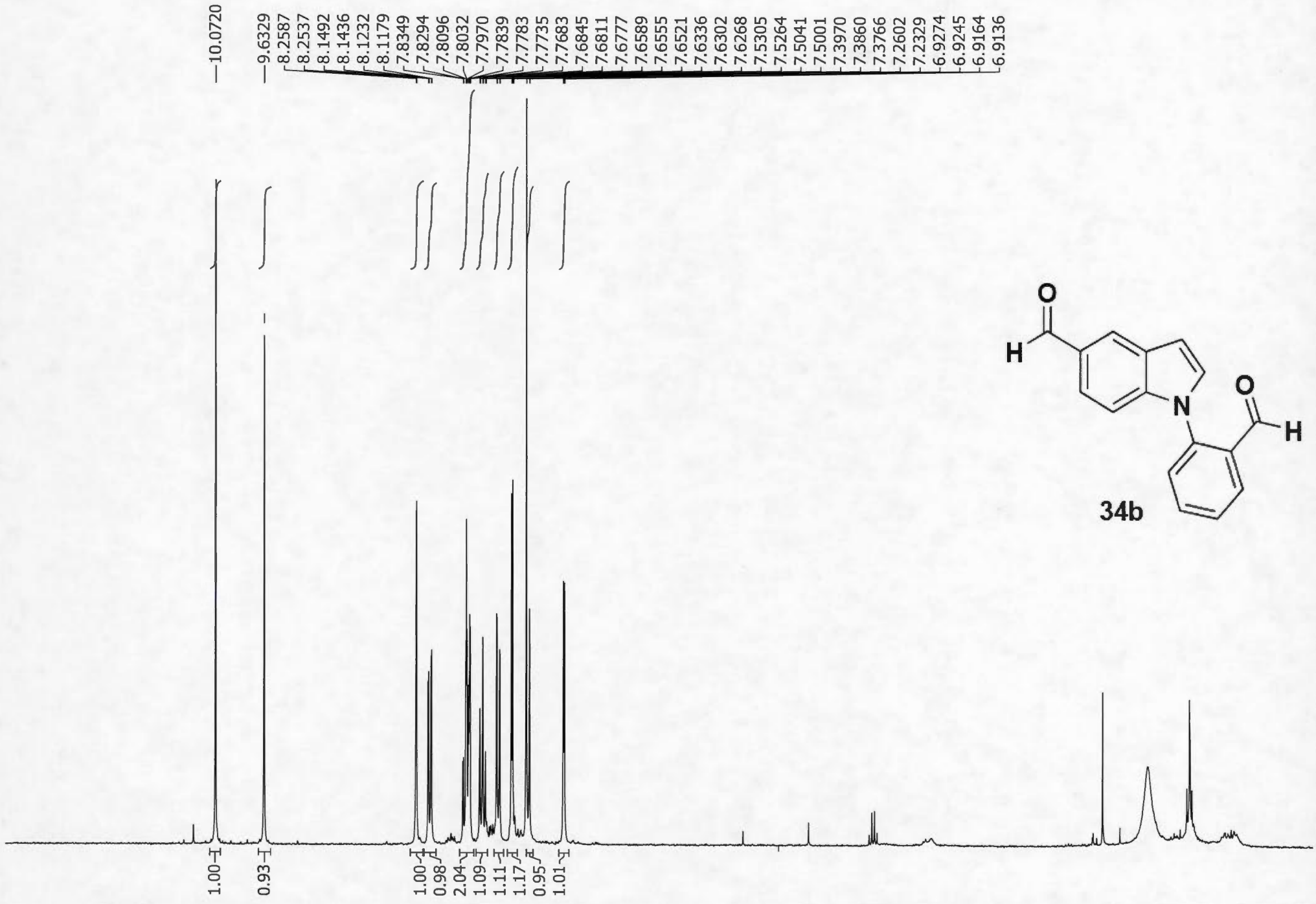

177.4028
159.5440
152.0538
146.9752
129.2268
129.1684
126.8799
124.4485
123.8530
122.3669
107.9689
70.1252
25.4905
H
O
O
OH
31a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

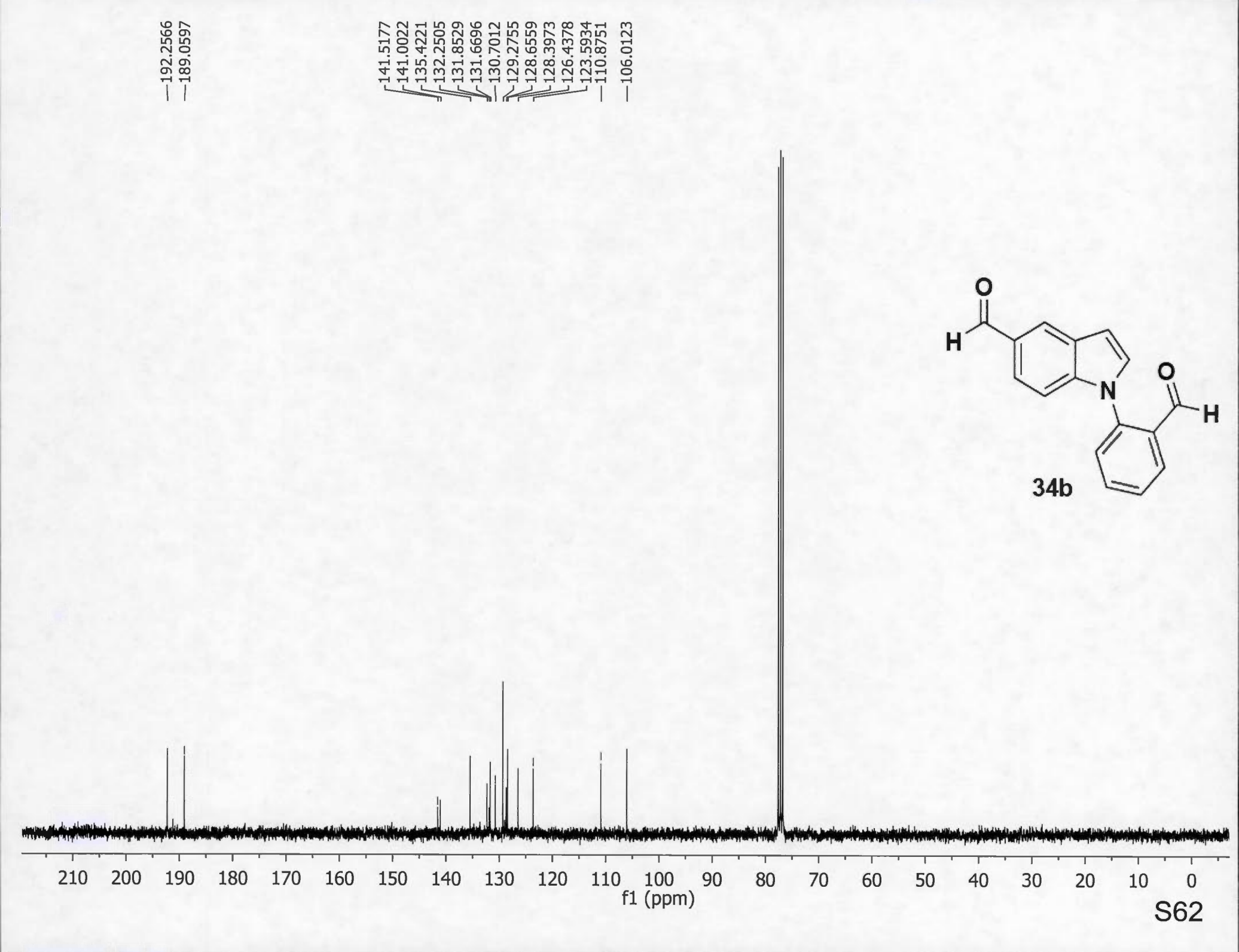

31a
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4000
3500
3000
2500
2000
1500
1000
3416,24
3102,67
2971,59
2916,34
2870,70
2821,27
1662,75
1516,36
1468,39
1426,17
1388,43
1264,53
1071,02
1027,69
968,09
792,00
767,11
696,70

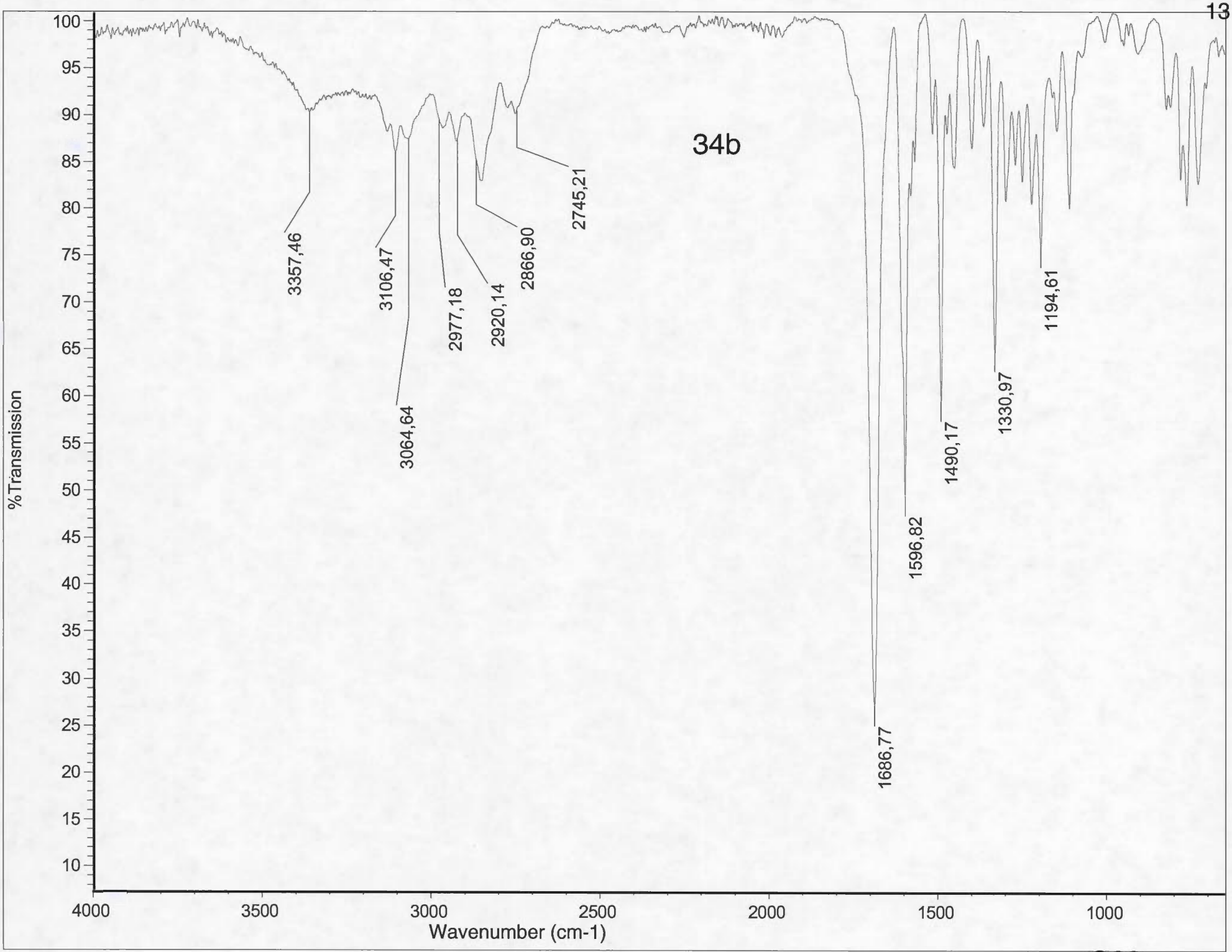

34a
10.0398
8.1935
7.5217
7.3855
7.3594
7.3557
7.2218
7.1938
6.7969
6.7866
5.4863
3.9832
3.9753
3.9450
3.9147
3.9070
3.6774
3.6397
2.0731
2.0461
2.0227
2.0099
1.9862
1.9210
1.9106
1.8970
1.7143
1.6723
1.6379
1.6232
1.6098
0.87
0.87
0.91
0.93
2.71
1.83
0.88
0.92
1.00
1.00
1.02
2.01
3.11

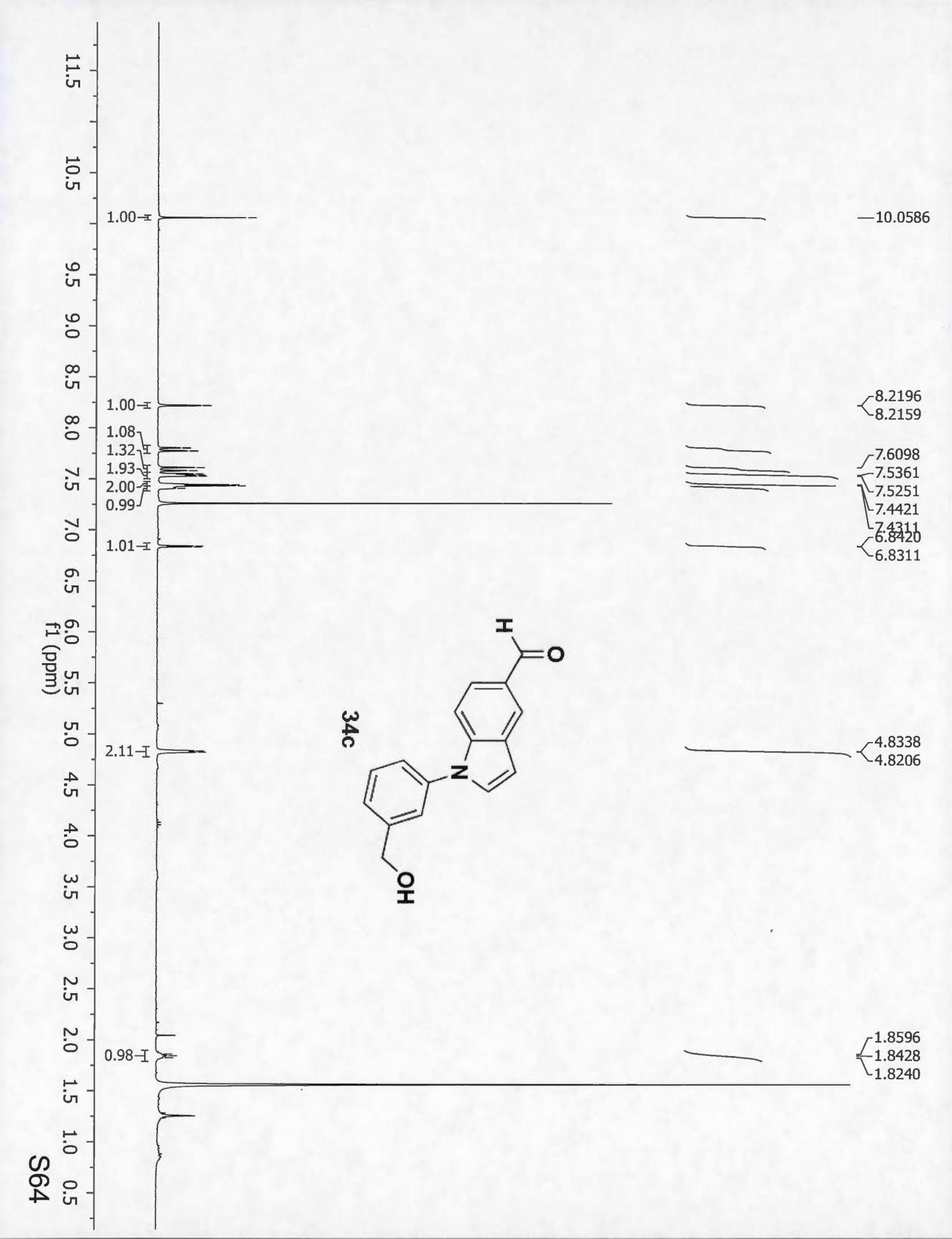

34a
H
O
N
O
O
192.5117
156.4572
139.7072
132.6700
130.4785
130.0321
128.8374
126.5149
126.1674
122.5793
117.6068
111.1701
104.8189
96.7321
62.2758
30.4178
25.2703
18.8118
f1 (ppm)

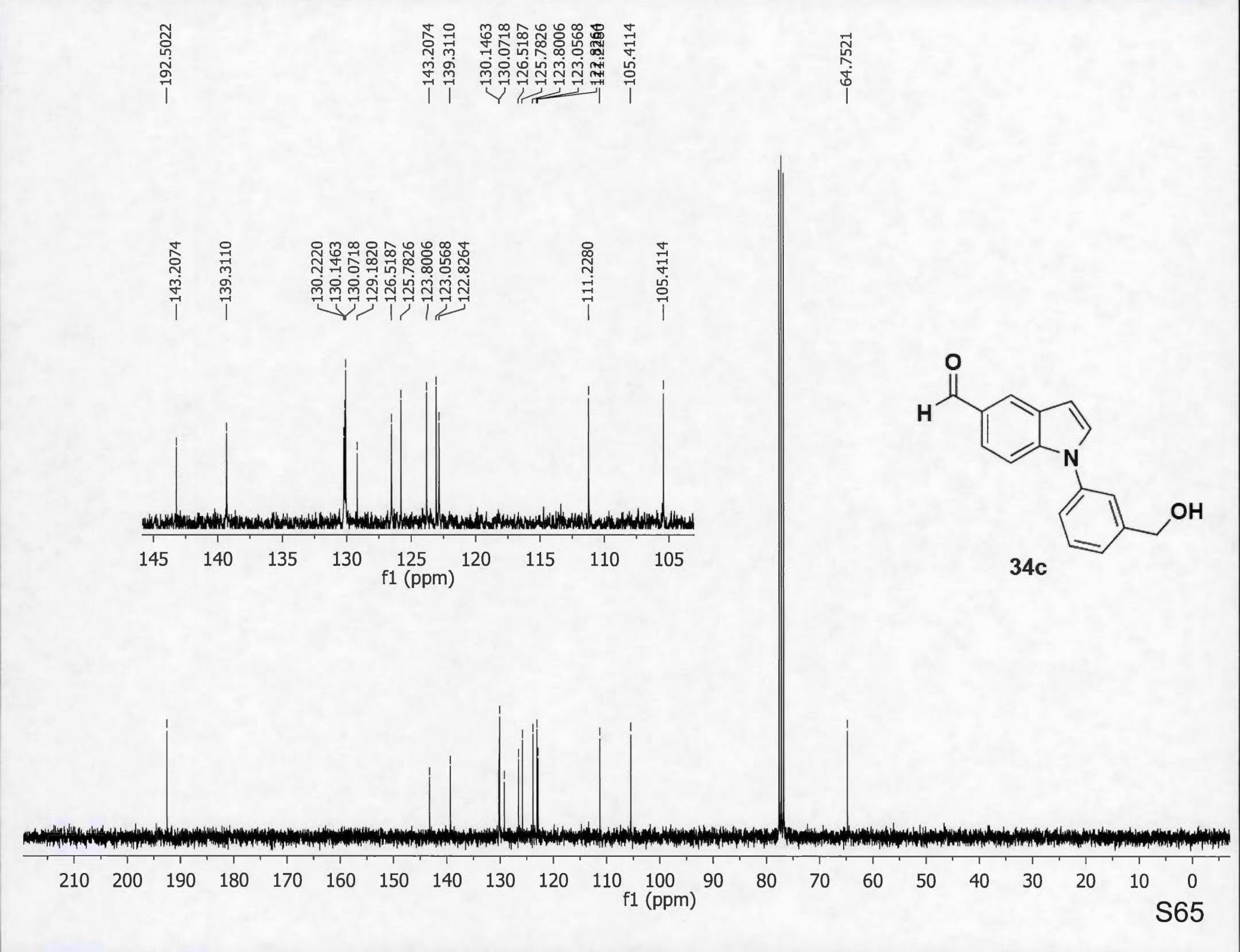

34a
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
4000
3500
3000
2500
2000
1500
1000
3355,65
3100,95
3039,20
2942,72
2873,26
2850,10
2715,03
1682,93
1615,18
1508,78
1456,96
1329,61
1237,34
1220,76
1200,80
1102,13
1044,03
920,54
731,45


10.0720
9.6329
8.2587
8.2537
8.1492
8.1436
8.1232
8.1179
7.8349
7.8294
7.8096
7.8032
7.7970
7.7839
7.7783
7.7735
7.7683
7.6845
7.6811
7.6777
7.6589
7.6555
7.6521
7.6336
7.6302
7.6268
7.5305
7.5264
7.5041
7.5001
7.3970
7.3860
7.3766
7.2602
7.2329
6.9274
6.9245
6.9164
6.9136
1.00
0.93
1.00
0.98
2.04
1.09
1.11
1.17
0.95
1.01
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
O
H
N
O
H
34b

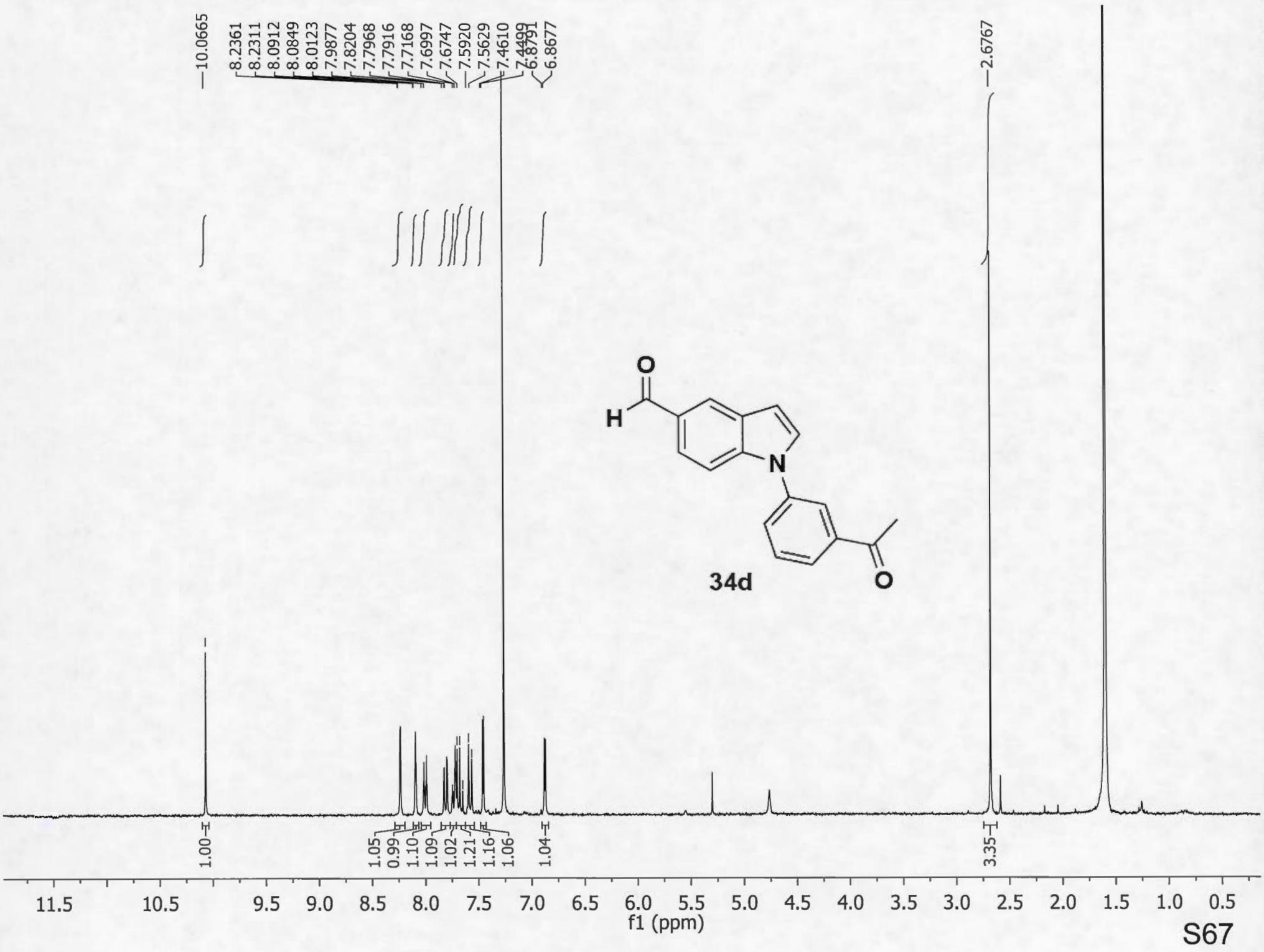

192.2566
189.0597
141.5177
141.0022
135.4221
132.2505
131.8529
131.6696
130.7012
129.2755
128.6559
128.3973
126.4378
123.5934
110.8751
106.0123
O
H
N
O
H
34b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

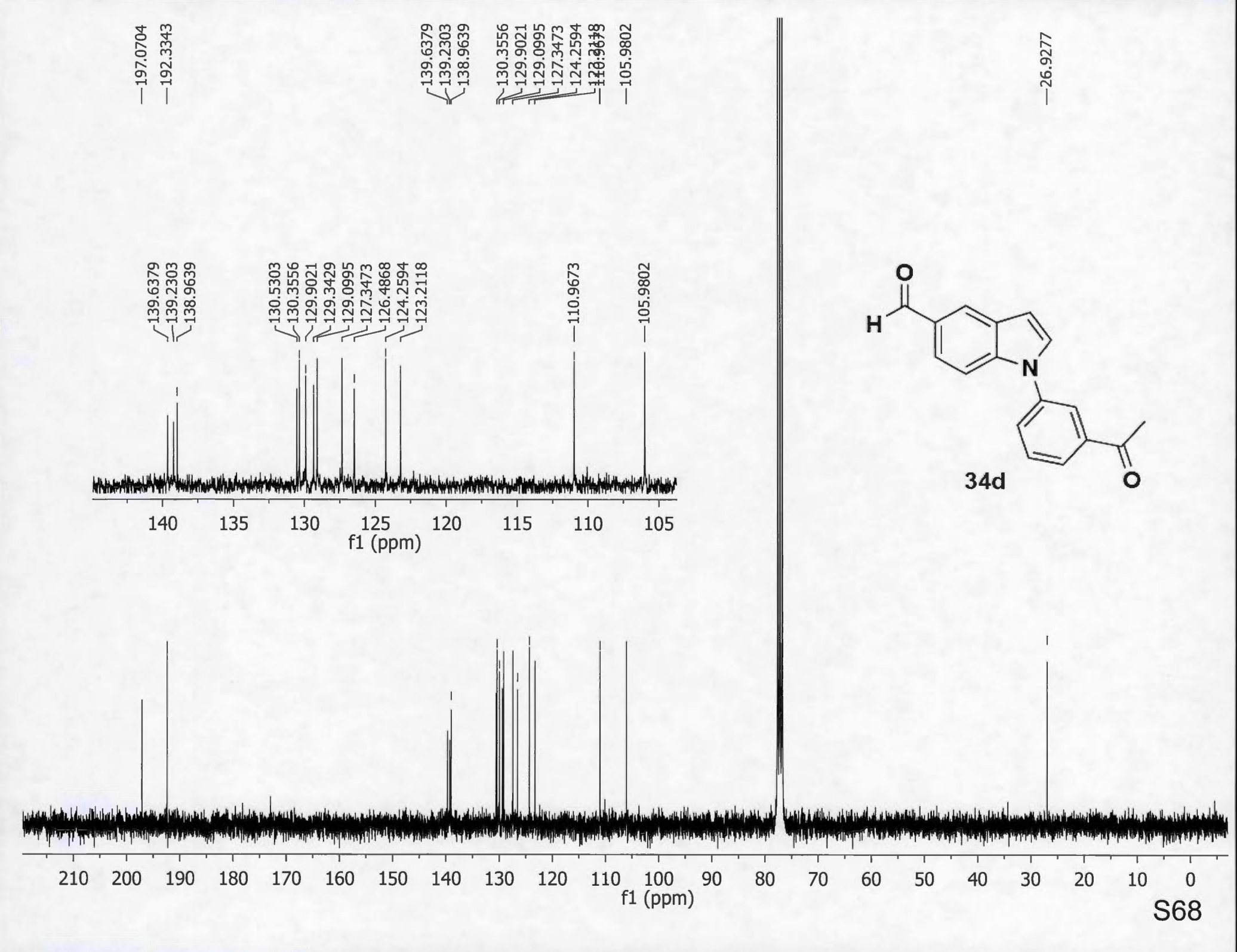

34b
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4000
3500
3000
2500
2000
1500
1000
3357,46
3106,47
3064,64
2977,18
2920,14
2866,90
2745,21
1686,77
1596,82
1490,17
1330,97
1194,61


11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
1.00
1.00
1.08
1.32
1.93
2.00
0.99
1.01
2.11
0.98
10.0586
8.2196
8.2159
7.6098
7.5361
7.5251
7.4421
7.4311
6.8420
6.8311
4.8338
4.8206
1.8596
1.8428
1.8240
34c
H
O
N
OH

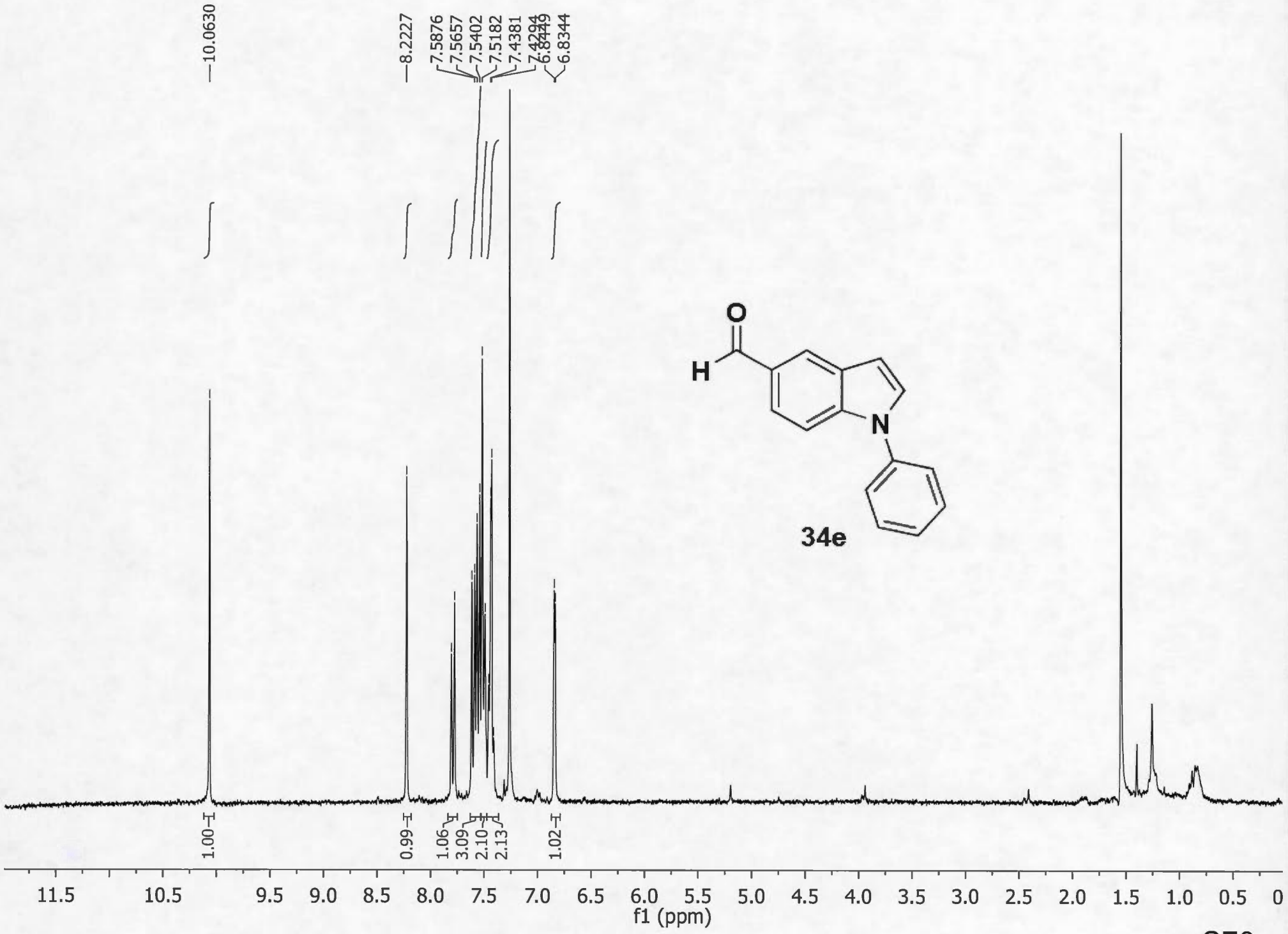

192.5022
143.2074
139.3110
130.1463
130.0718
126.5187
125.7826
123.8006
123.0568
105.4114
64.7521
143.2074
139.3110
130.2220
130.1463
130.0718
129.1820
126.5187
125.7826
123.8006
123.0568
122.8264
111.2280
105.4114
145 140 135 130 125 120 115 110 105
f1 (ppm)
O
H
N
OH
34c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

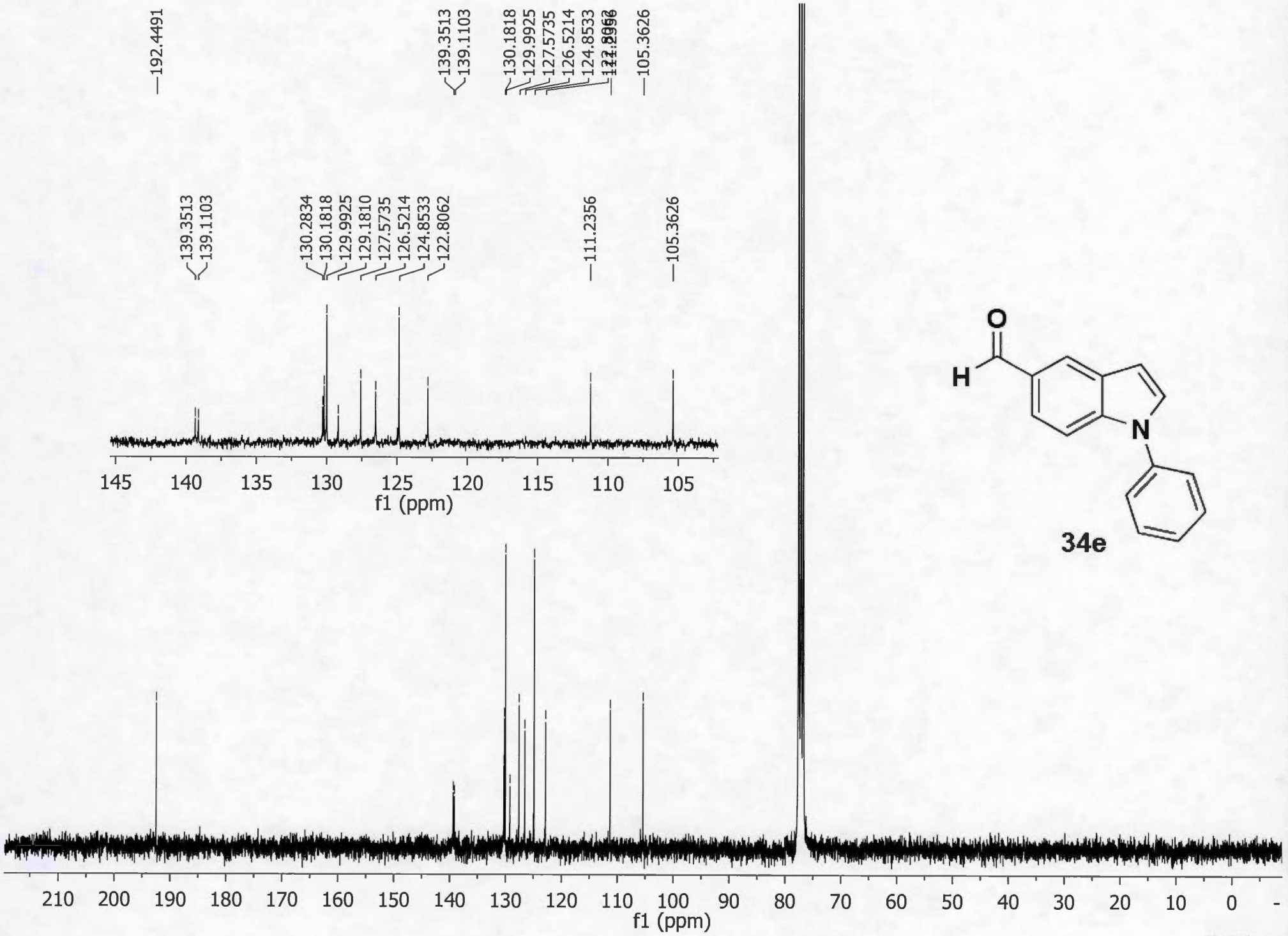
%Transmission
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
3411,11
3104,81
3054,64
2919,57
2726,61
2857,82
2815,37
2788,36
34c
1681,98
1601,94
1588,58
1565,05
1492,73
1448,53
1331,02
1223,01
1103,06
1032,46
893,53
726,10
698,48

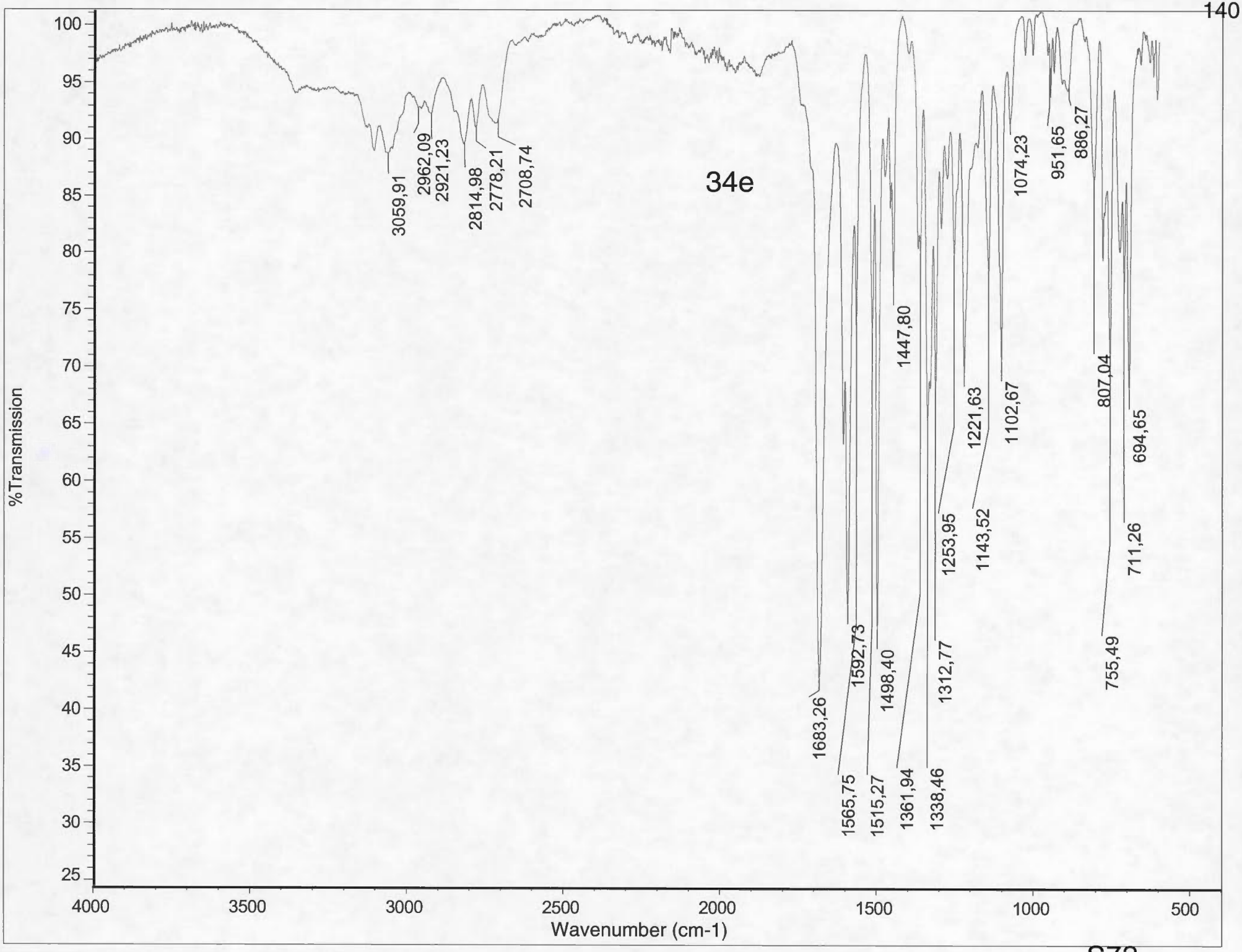

10.0665
8.2361
8.2311
8.0912
8.0849
8.0123
7.9877
7.8204
7.7968
7.7916
7.7168
7.6997
7.6747
7.5920
7.5629
7.4610
7.4499
6.8791
6.8677
2.6767
O
H
N
O
34d
1.00
1.05
0.99
1.10
1.09
1.02
1.21
1.16
1.06
1.04
3.35
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

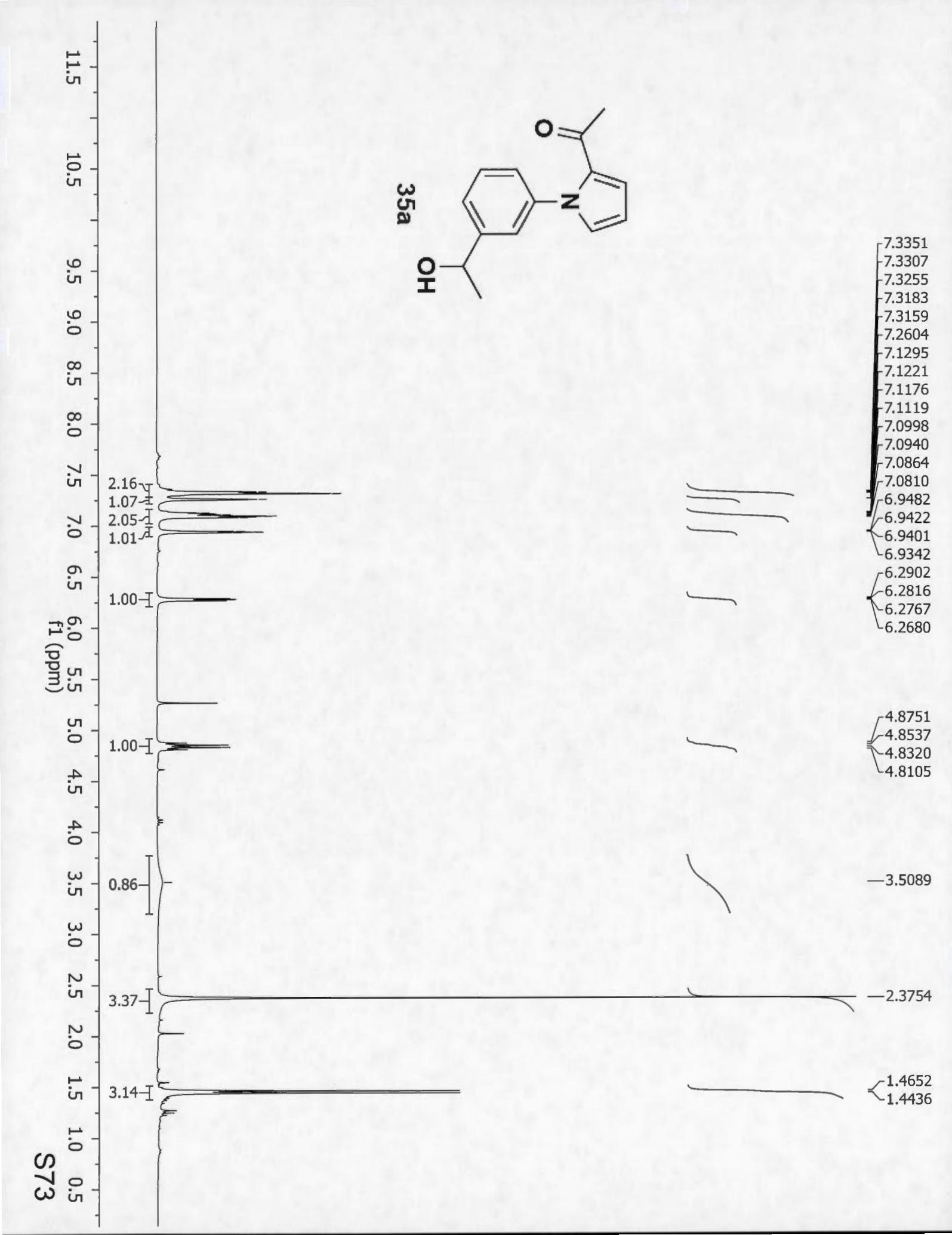

197.0704
192.3343
139.6379
139.2303
138.9639
130.3556
129.9021
129.0995
127.3473
124.2594
123.2118
110.9673
105.9802
26.9277
139.6379
139.2303
138.9639
130.5303
130.3556
129.9021
129.3429
129.0995
127.3473
126.4868
124.2594
123.2118
110.9673
105.9802
140
135
130
125
120
115
110
105
f1 (ppm)
O
H
N
O
34d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

%Transmission
Wavenumber (cm-1)
3357,46
3102,67
3057,04
2923,94
2825,07
2741,41
34d
1682,35
1599,17
1586,22
1491,10
1445,08
1356,63
1329,70
1297,56
1268,64
1235,79
1105,18
768,81

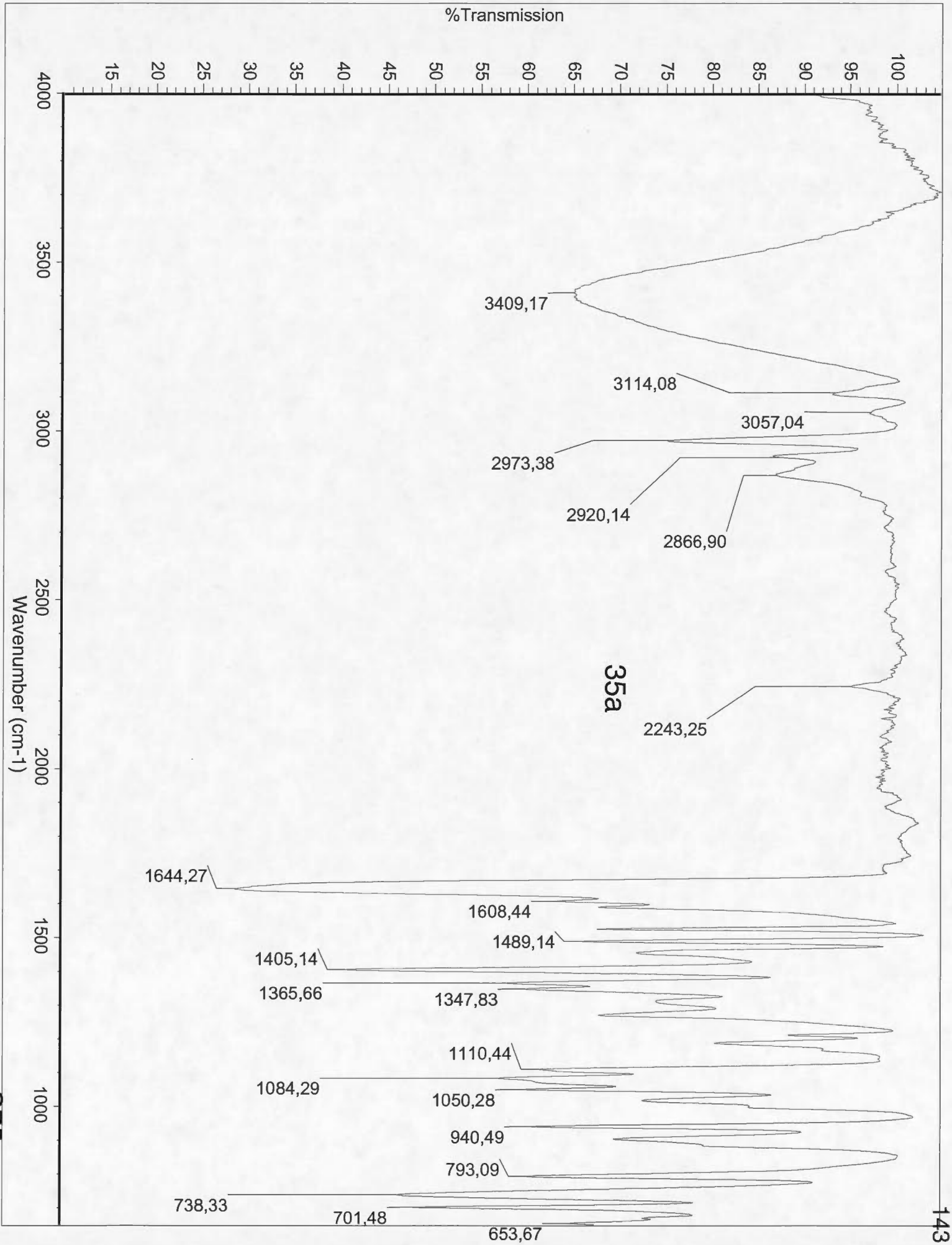

10.0630
8.2227
7.5876
7.5657
7.5402
7.5182
7.4381
7.4294
6.8449
6.8344
O
H
N
34e
1.00
0.99
1.06
3.09
2.10
2.13
1.02
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

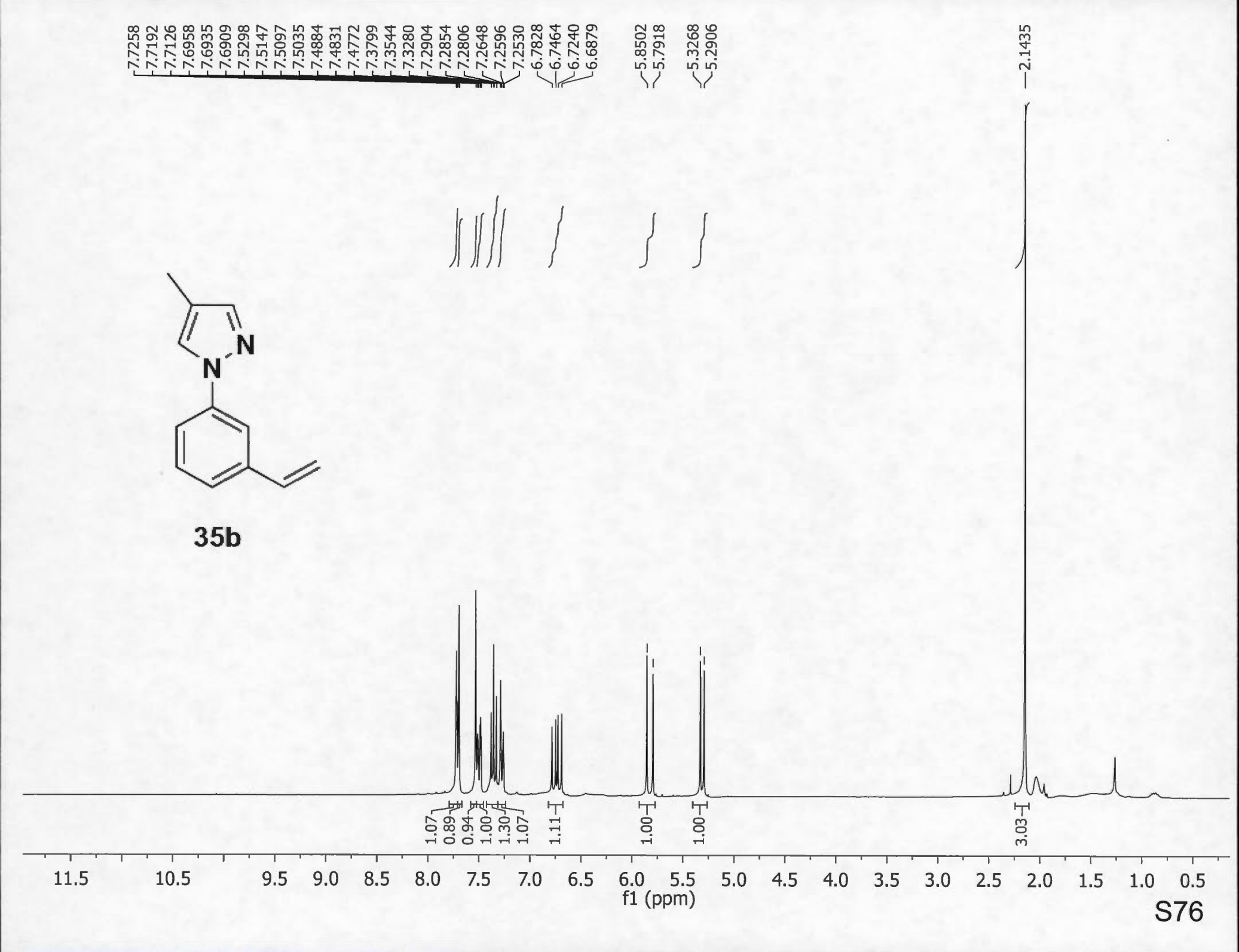

192.4491
139.3513
139.1103
130.1818
129.9925
127.5735
126.5214
124.8533
105.3626
139.3513
139.1103
130.2834
130.1818
129.9925
129.1810
127.5735
126.5214
124.8533
122.8062
111.2356
105.3626
145 140 135 130 125 120 115 110 105
f1 (ppm)
O
H
N
34e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -
f1 (ppm)

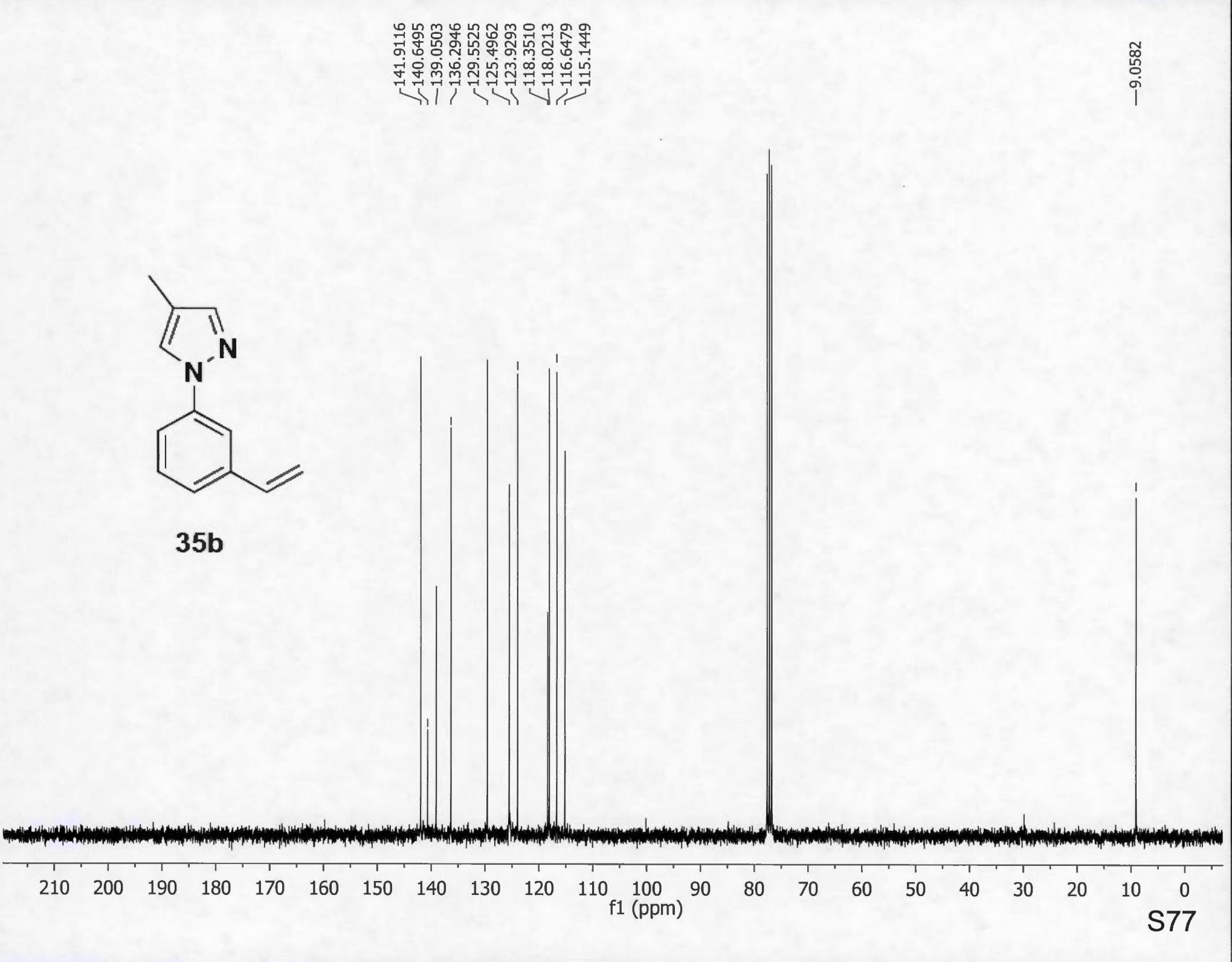

34e
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
4000
3500
3000
2500
2000
1500
1000
500
3059,91
2962,09
2921,23
2814,98
2778,21
2708,74
1683,26
1592,73
1565,75
1515,27
1498,40
1447,80
1361,94
1338,46
1312,77
1253,95
1221,63
1143,52
1102,67
1074,23
951,65
886,27
807,04
755,49
711,26
694,65


35a
O
N
OH
7.3351
7.3307
7.3255
7.3183
7.3159
7.2604
7.1295
7.1221
7.1176
7.1119
7.0998
7.0940
7.0864
7.0810
6.9482
6.9422
6.9401
6.9342
6.2902
6.2816
6.2767
6.2680
4.8751
4.8537
4.8320
4.8105
3.5089
2.3754
1.4652
1.4436
2.16
1.07
2.05
1.01
1.00
1.00
0.86
3.37
3.14
f1 (ppm)

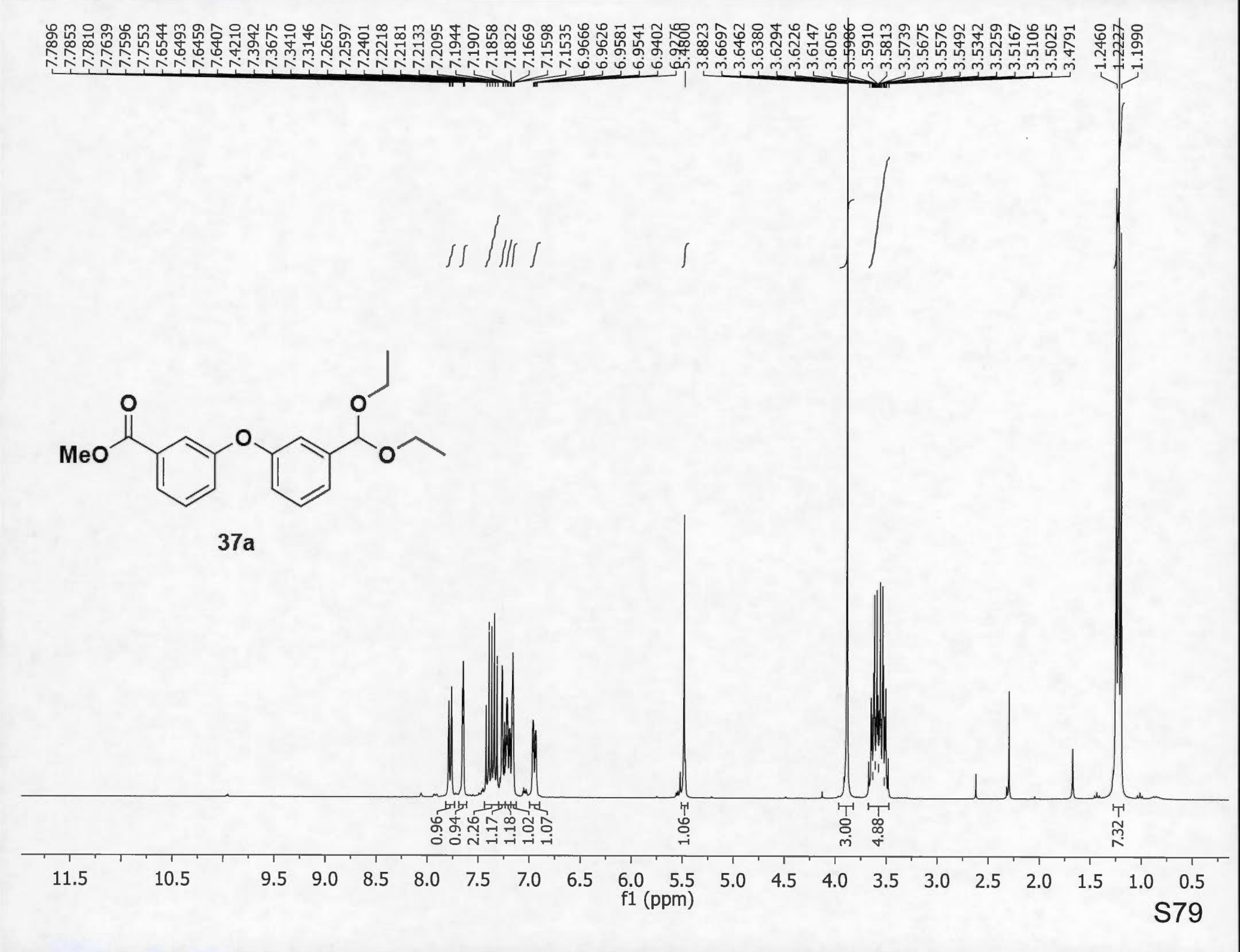
35a
O
N
OH
187.4698
147.0561
140.8318
131.4480
131.4256
128.5649
124.8469
124.6832
123.3495
120.9097
109.2854
69.5820
27.1991
25.0454
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

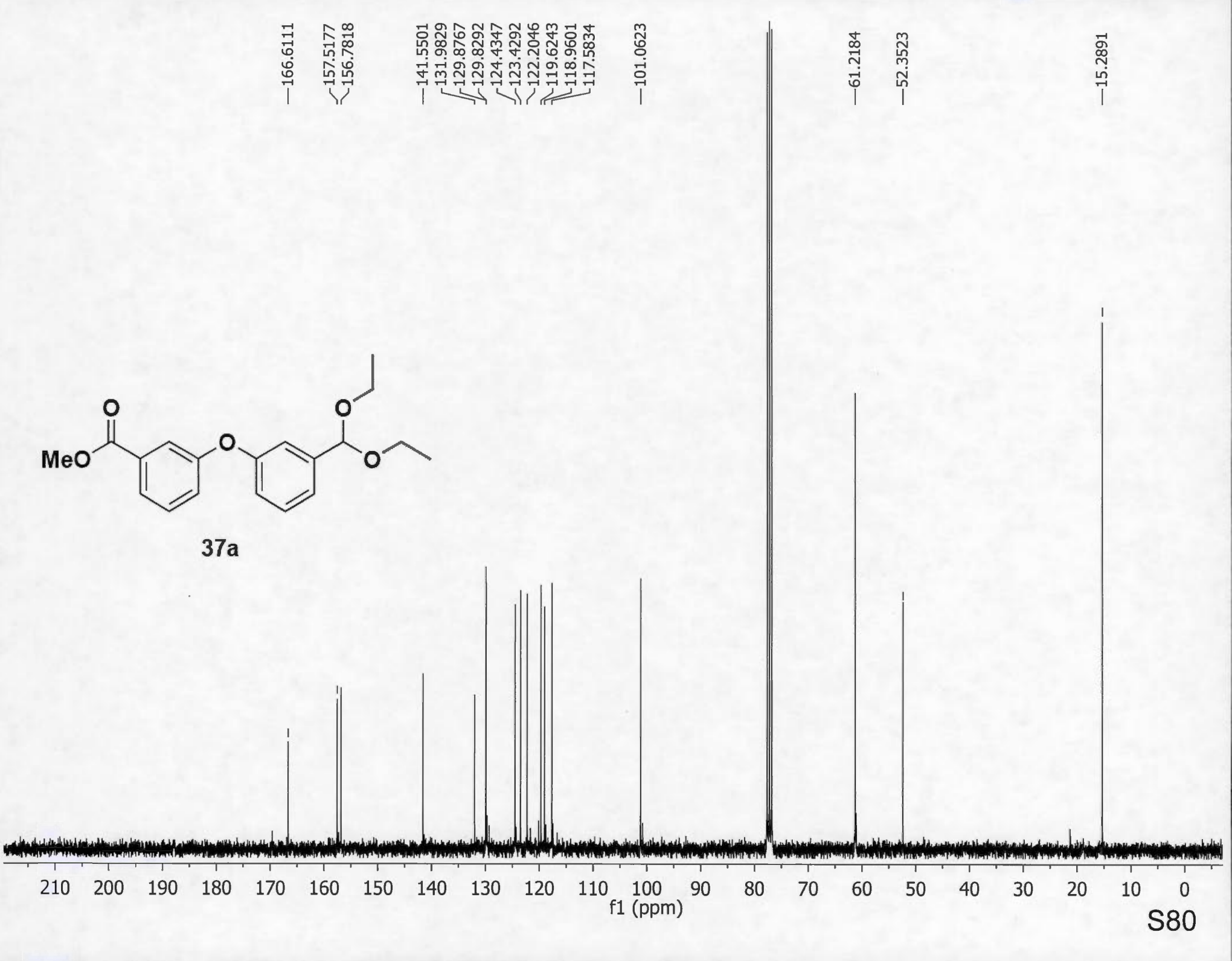

%Transmission
Wavenumber (cm-1)
3409,17
3114,08
3057,04
2973,38
2920,14
2866,90
2243,25
1644,27
1608,44
1489,14
1405,14
1365,66
1347,83
1110,44
1084,29
1050,28
940,49
793,09
738,33
701,48
653,67
35a


7.7258
7.7192
7.7126
7.6958
7.6935
7.6909
7.5298
7.5147
7.5097
7.5035
7.4884
7.4831
7.4772
7.3799
7.3544
7.3280
7.2904
7.2854
7.2806
7.2648
7.2596
7.2530
6.7828
6.7464
6.7240
6.6879
5.8502
5.7918
5.3268
5.2906
2.1435
N
N
35b
1.07
0.89
0.94
1.00
1.30
1.07
1.11
1.00
1.00
3.03
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

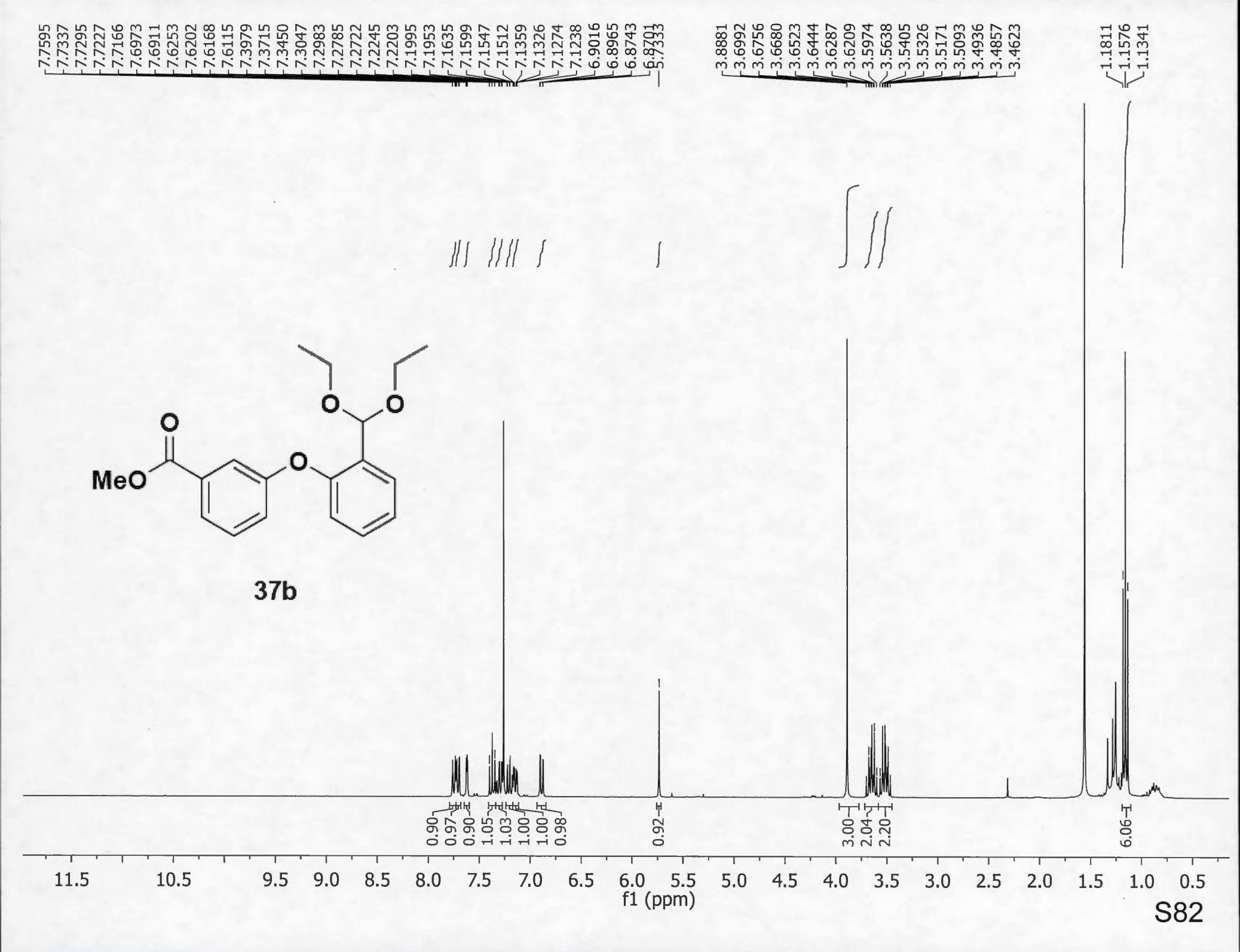

141.9116
140.6495
139.0503
136.2946
129.5525
125.4962
123.9293
118.3510
118.0213
116.6479
115.1449
9.0582
N
N
35b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

%Transmission
40
45
50
55
60
65
70
75
80
85
90
95
100
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
3289,01
3140,70
3117,88
3064,64
2926,34
2863,10
35b
1695,20
1605,88
1585,38
1533,38
1488,99
1454,03
1399,59
1362,27
1255,39
1229,12
1046,97
790,96
755,01
696,69

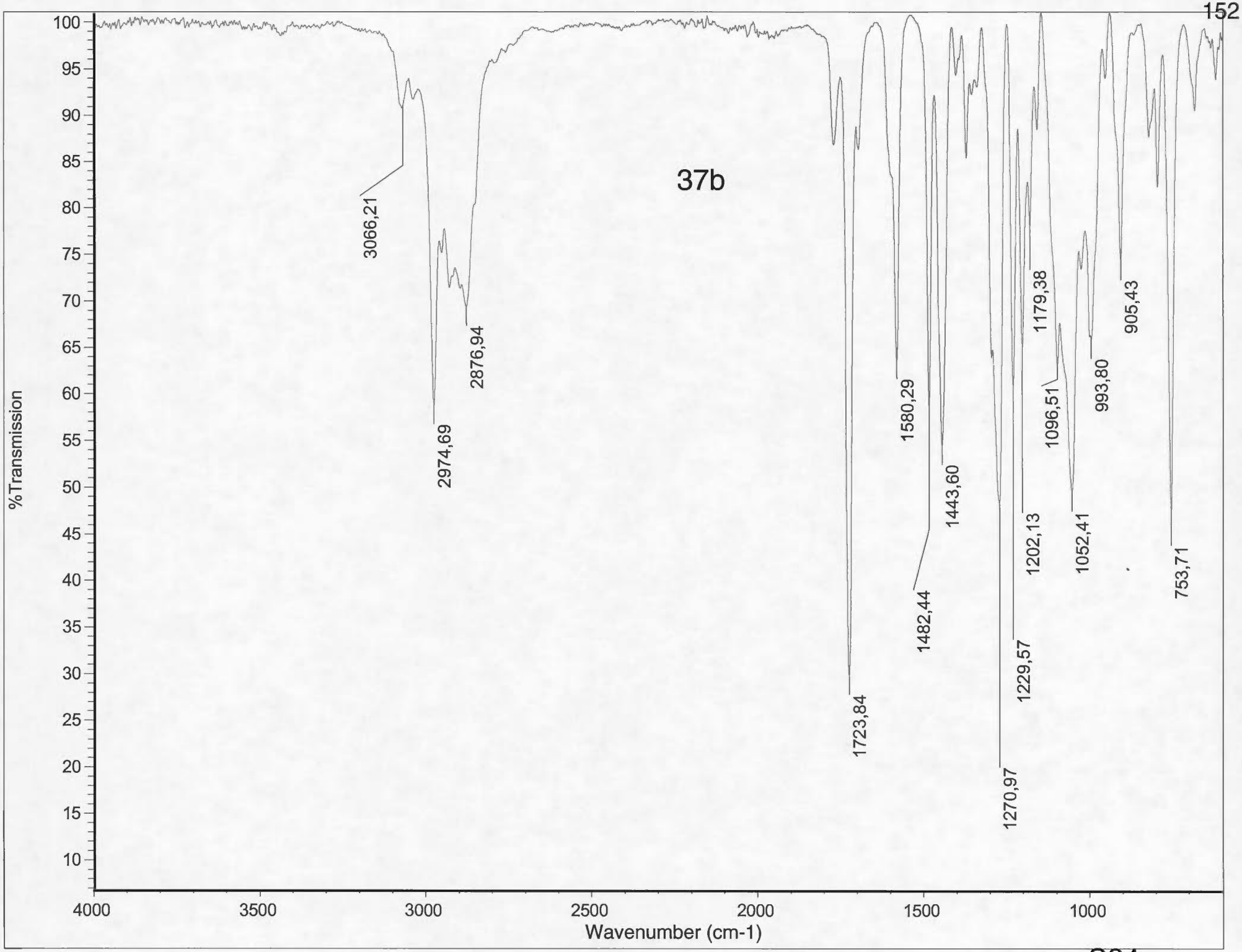

7.7896
7.7853
7.7810
7.7639
7.7596
7.7553
7.6544
7.6493
7.6459
7.6407
7.4210
7.3942
7.3675
7.3410
7.3146
7.2657
7.2597
7.2401
7.2218
7.2181
7.2133
7.2095
7.1944
7.1907
7.1858
7.1822
7.1669
7.1598
7.1535
6.9666
6.9626
6.9581
6.9541
6.9402
6.9276
5.4800
3.8823
3.6697
3.6462
3.6380
3.6294
3.6226
3.6147
3.6056
3.5986
3.5910
3.5813
3.5739
3.5675
3.5576
3.5492
3.5342
3.5259
3.5167
3.5106
3.5025
3.4791
1.2460
1.2227
1.1990
MeO
O
O
O
O
37a
0.96
0.94
2.26
1.17
1.18
1.02
1.07
1.06
3.00
4.88
7.32
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

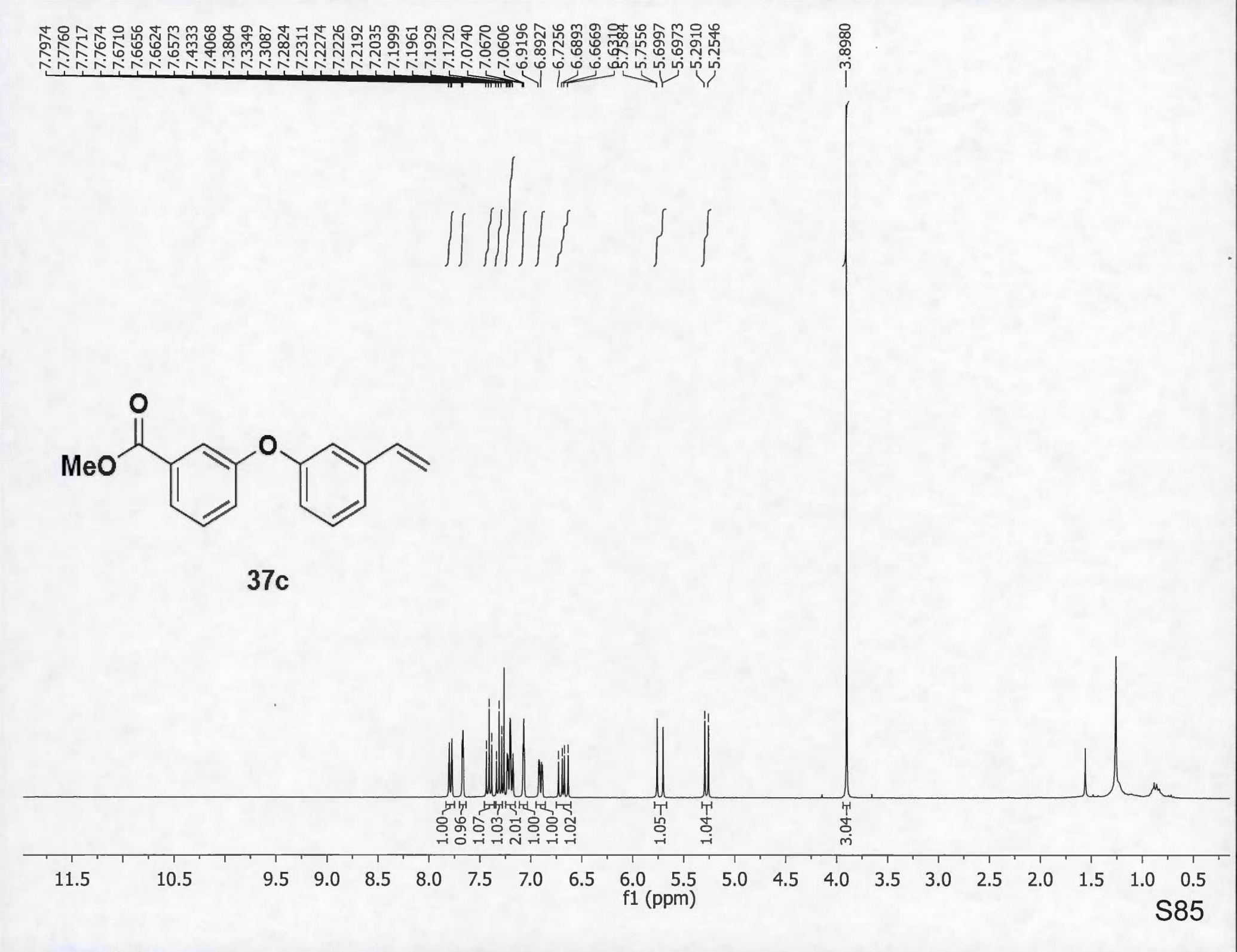

166.6111
157.5177
156.7818
141.5501
131.9829
129.8767
129.8292
124.4347
123.4292
122.2046
119.6243
118.9601
117.5834
101.0623
61.2184
52.3523
15.2891
MeO
O
O
O
O
37a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

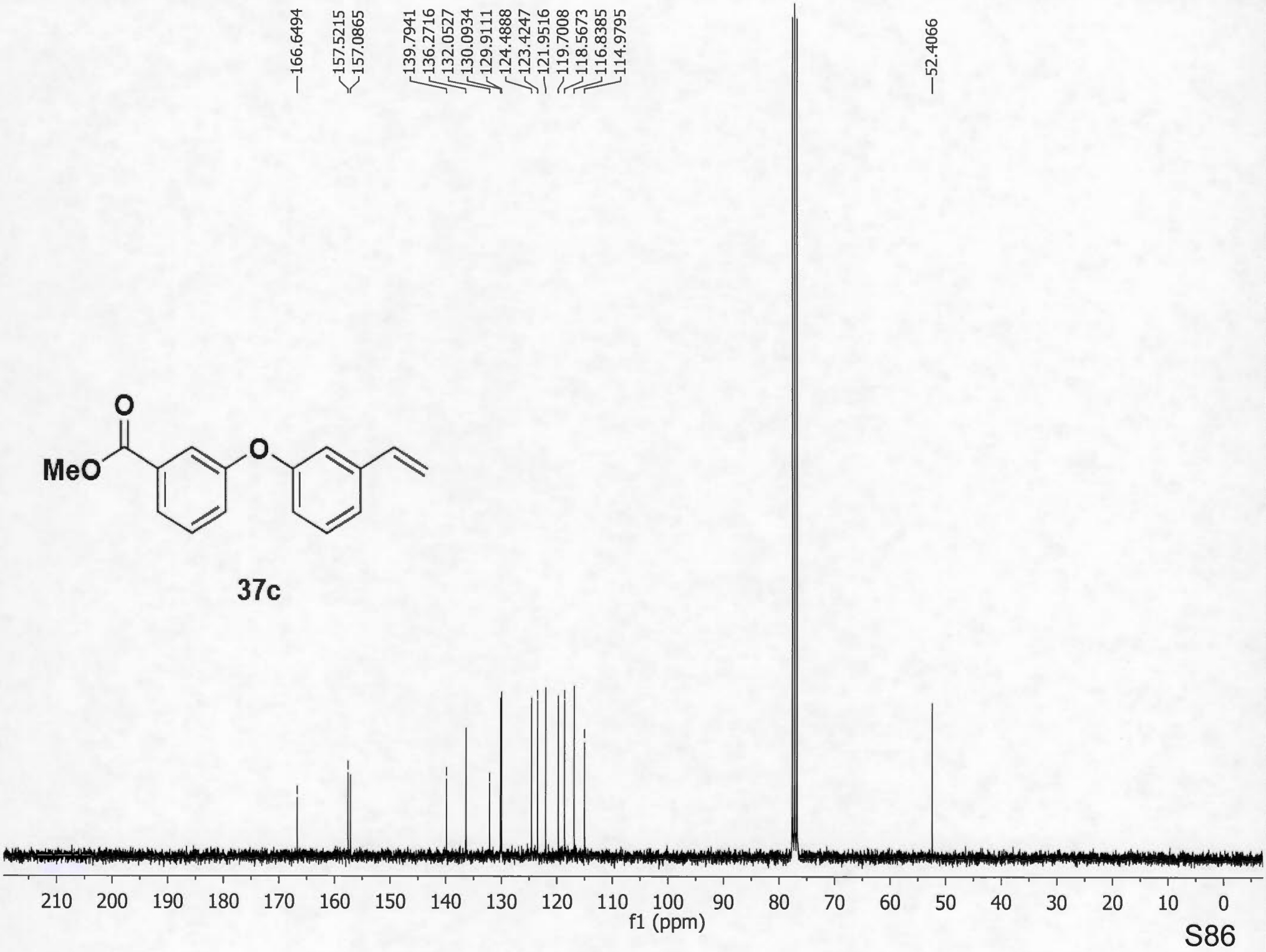
%Transmission
40
45
50
55
60
65
70
75
80
85
90
95
100
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
3068,45
2973,38
2920,14
2878,31
1726,07
1684,24
1581,57
1482,70
1440,87
1357,21
1269,74
1049,18
900,88
794,40
752,57
695,53
37a

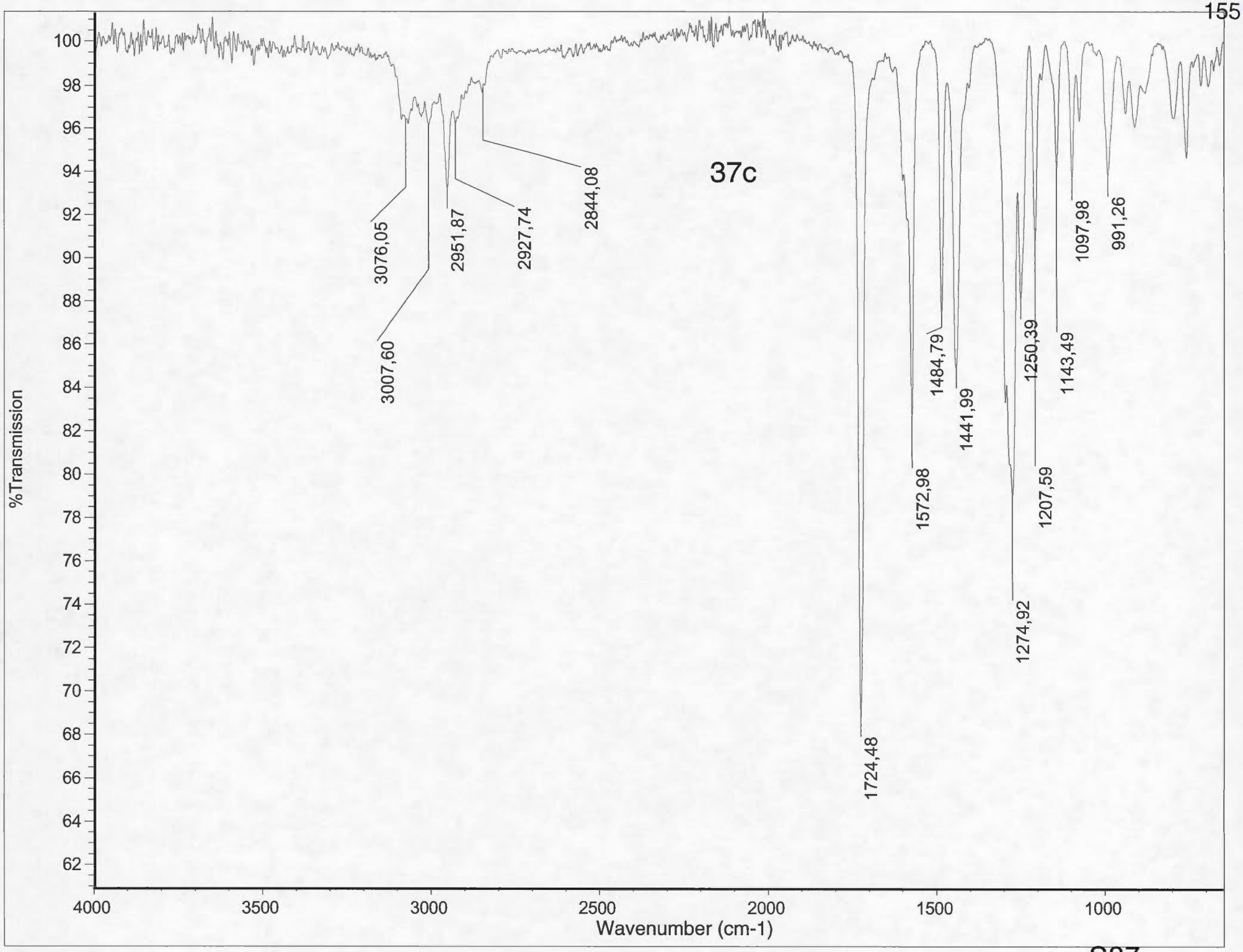

7.7595
7.7337
7.7295
7.7227
7.7166
7.6973
7.6911
7.6253
7.6202
7.6168
7.6115
7.3979
7.3715
7.3450
7.3047
7.2983
7.2785
7.2722
7.2245
7.2203
7.1995
7.1953
7.1635
7.1599
7.1547
7.1512
7.1359
7.1326
7.1274
7.1238
6.9016
6.8965
6.8743
6.8701
5.7333
3.8881
3.6992
3.6756
3.6680
3.6523
3.6444
3.6287
3.6209
3.5974
3.5638
3.5405
3.5326
3.5171
3.5093
3.4936
3.4857
3.4623
1.1811
1.1576
1.1341
MeO
O
O
O
O
37b
0.90
0.97
0.90
1.05
1.03
1.00
1.00
0.98
0.92
3.00
2.04
2.20
6.06
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

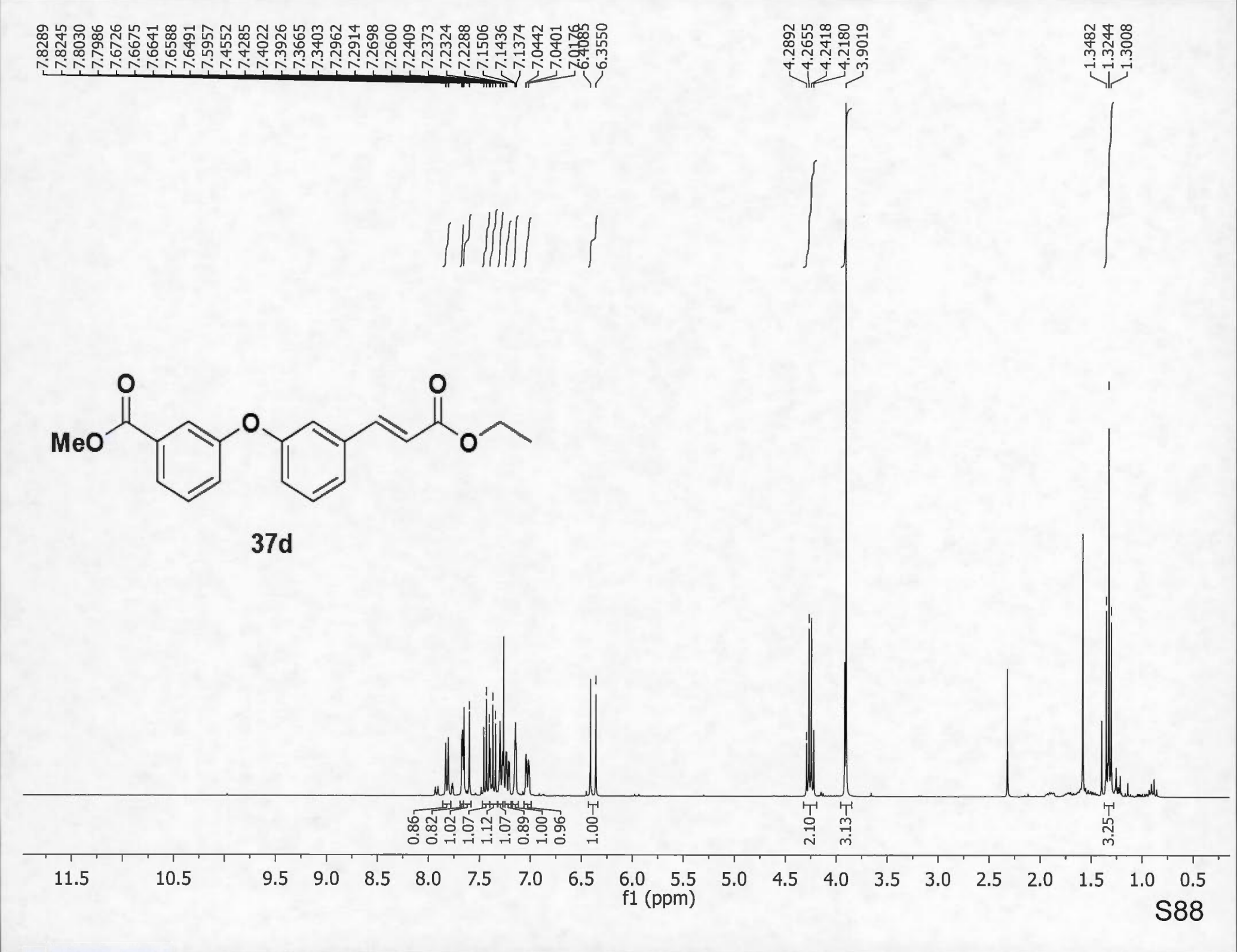
37b
MeO
O
O
O
O
166.6628
158.1920
153.8284
131.9293
131.1939
129.9231
129.7332
128.0085
124.3853
124.0499
122.5804
119.7274
118.9695
97.6211
62.4533
52.3234
15.2183
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

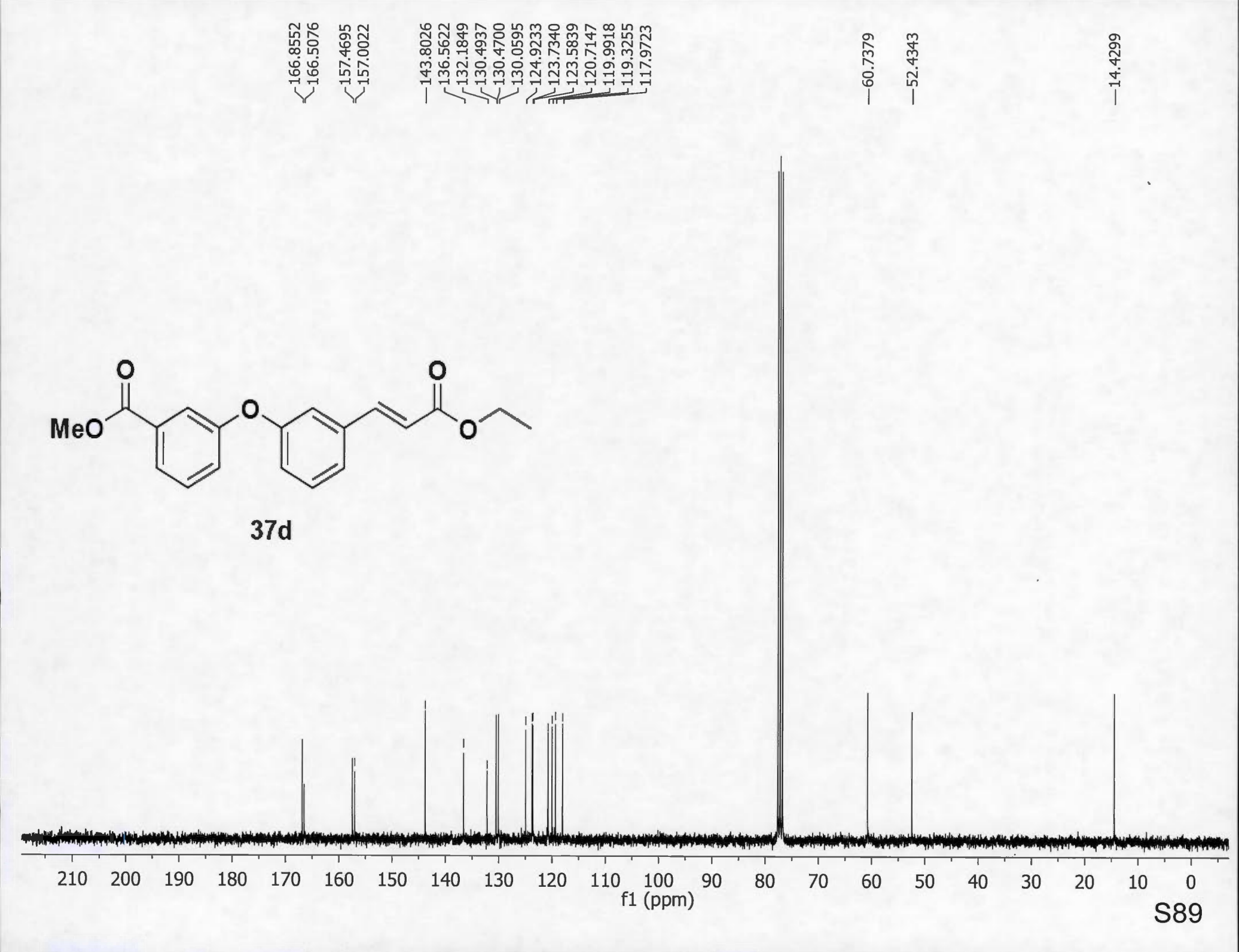

37b
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4000
3500
3000
2500
2000
1500
1000
3066,21
2974,69
2876,94
1723,84
1580,29
1482,44
1443,60
1270,97
1229,57
1202,13
1179,38
1096,51
1052,41
993,80
905,43
753,71

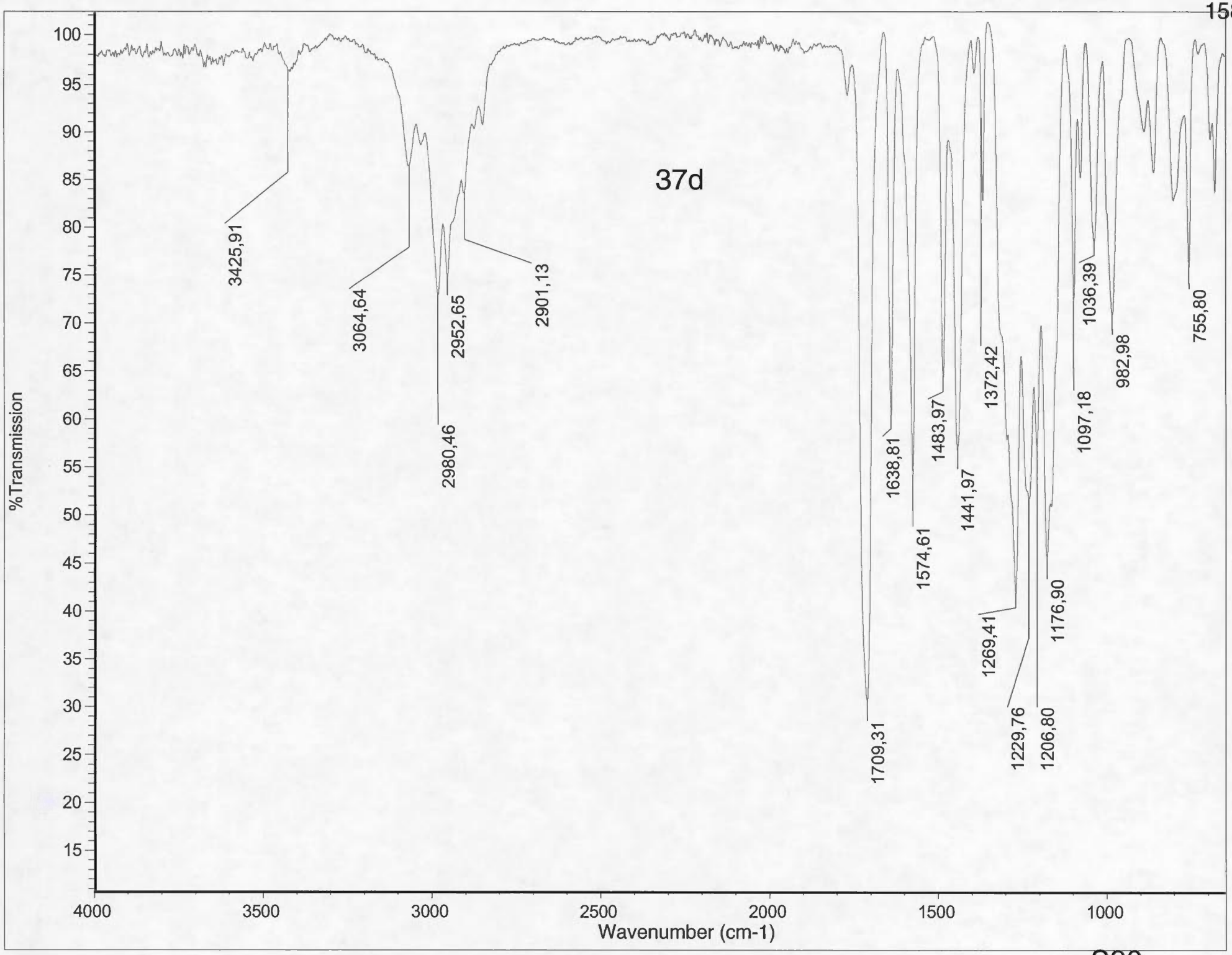

7.7974
7.7760
7.7717
7.7674
7.6710
7.6656
7.6624
7.6573
7.4333
7.4068
7.3804
7.3349
7.3087
7.2824
7.2311
7.2274
7.2226
7.2192
7.2035
7.1999
7.1961
7.1929
7.1720
7.0740
7.0670
7.0606
6.9196
6.8927
6.7256
6.6893
6.6669
6.6310
5.7584
5.7556
5.6997
5.6973
5.2910
5.2546
3.8980
MeO
O
O
37c
1.00
0.96
1.07
1.03
2.01
1.00
1.00
1.02
1.05
1.04
3.04
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

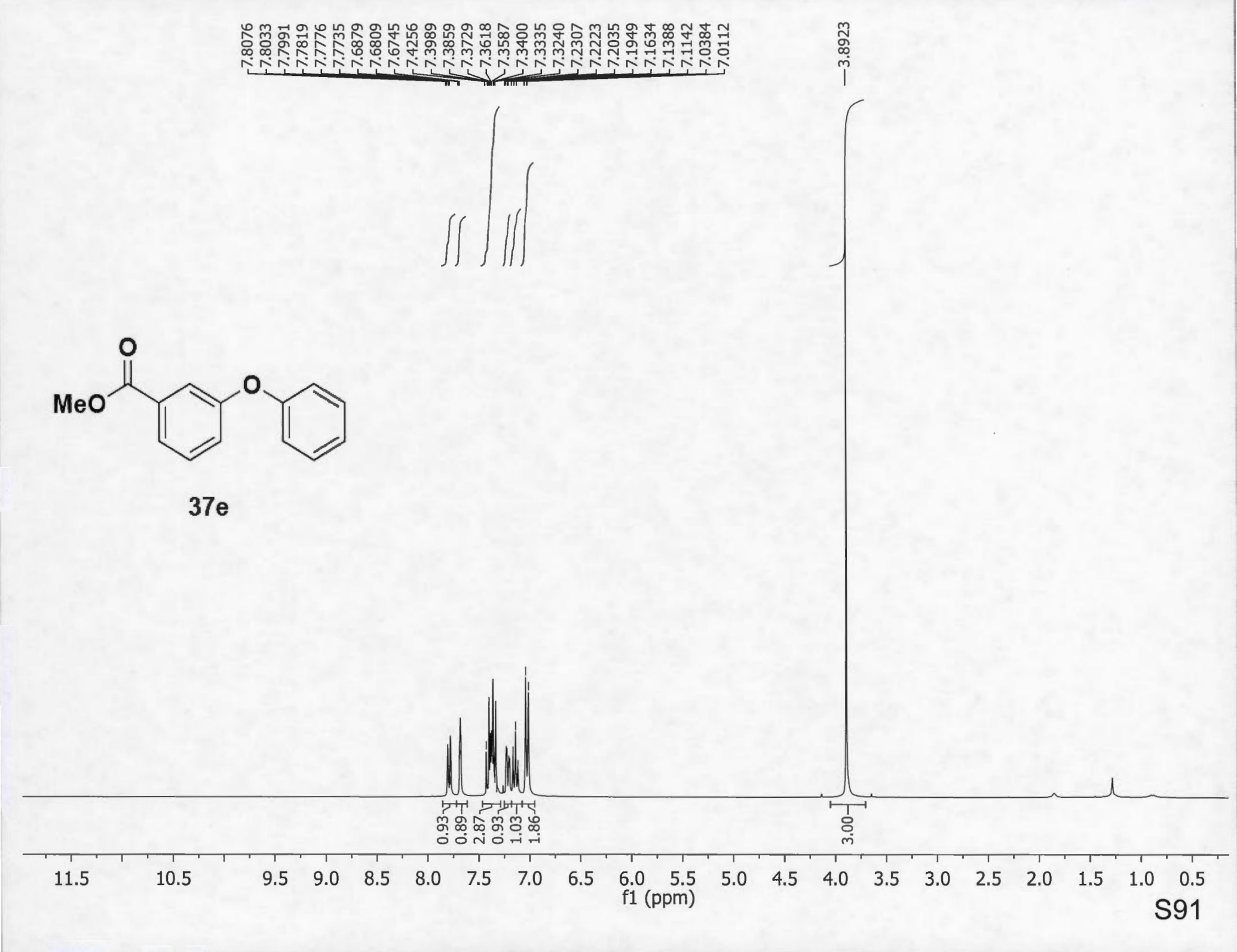

166.6494
157.5215
157.0865
139.7941
136.2716
132.0527
130.0934
129.9111
124.4888
123.4247
121.9516
119.7008
118.5673
116.8385
114.9795
52.4066
MeO
O
O
37c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

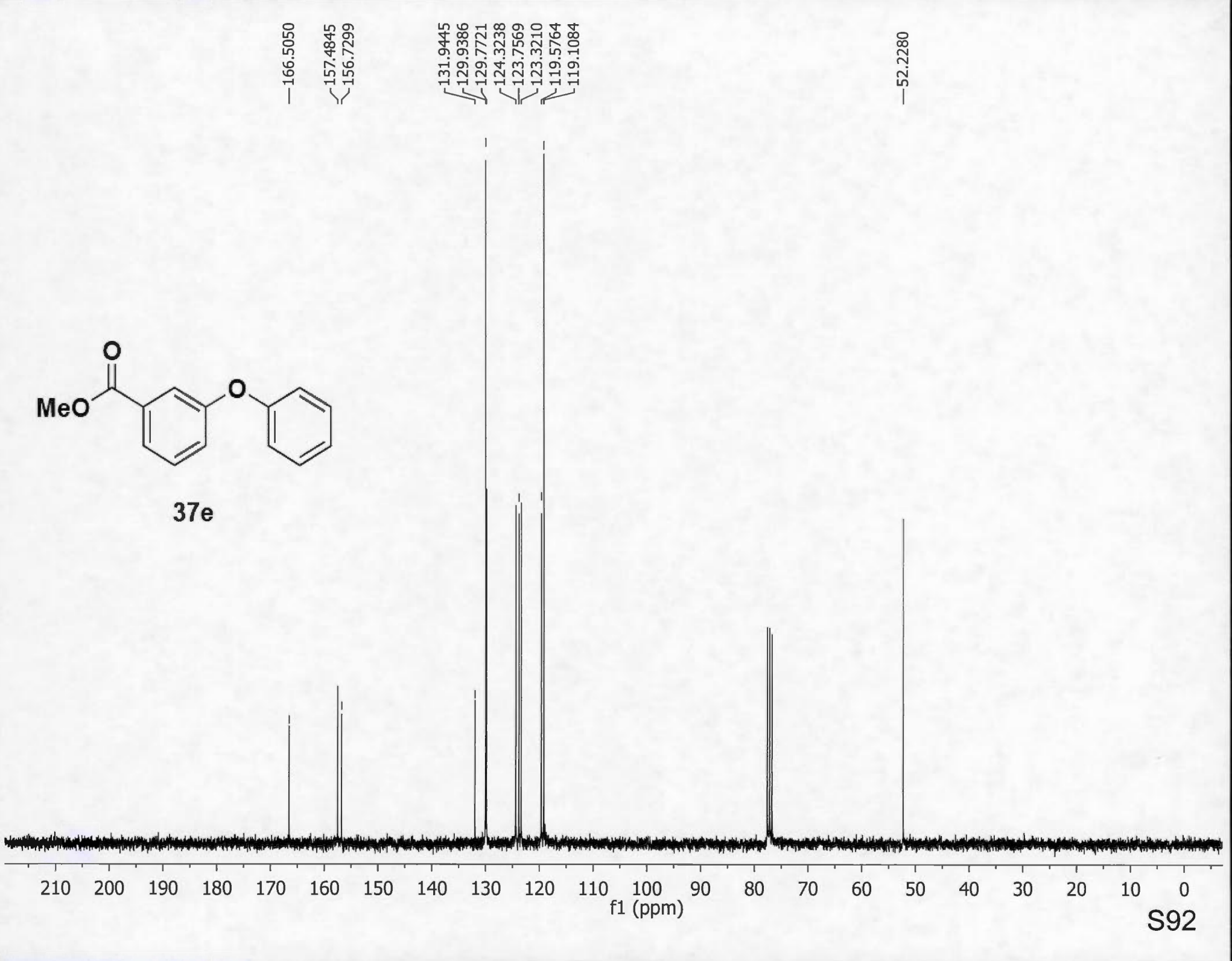

37c
%Transmission
Wavenumber (cm-1)
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
4000
3500
3000
2500
2000
1500
1000
3076,05
3007,60
2951,87
2927,74
2844,08
1724,48
1572,98
1484,79
1441,99
1274,92
1250,39
1207,59
1143,49
1097,98
991,26


7.8289
7.8245
7.8030
7.7986
7.6726
7.6675
7.6641
7.6588
7.6491
7.5957
7.4552
7.4285
7.4022
7.3926
7.3665
7.3403
7.2962
7.2914
7.2698
7.2600
7.2409
7.2373
7.2324
7.2288
7.1506
7.1436
7.1374
7.0442
7.0401
7.0176
6.4085
6.3550
4.2892
4.2655
4.2418
4.2180
3.9019
1.3482
1.3244
1.3008
MeO
O
O
O
O
37d
0.86
0.82
1.02
1.07
1.12
1.07
0.89
1.00
0.96
1.00
2.10
3.13
3.25
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


166.8552
166.5076
157.4695
157.0022
143.8026
136.5622
132.1849
130.4937
130.4700
130.0595
124.9233
123.7340
123.5839
120.7147
119.9918
119.3255
117.9723
60.7379
52.4343
14.4299
MeO
O
O
O
O
37d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


37d
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
4000
3500
3000
2500
2000
1500
1000
3425,91
3064,64
2980,46
2952,65
2901,13
1709,31
1638,81
1574,61
1483,97
1441,97
1372,42
1269,41
1229,76
1206,80
1176,90
1097,18
1036,39
982,98
755,80


7.8076
7.8033
7.7991
7.7819
7.7776
7.7735
7.6879
7.6809
7.6745
7.4256
7.3989
7.3859
7.3729
7.3618
7.3587
7.3400
7.3335
7.3240
7.2307
7.2223
7.2035
7.1949
7.1634
7.1388
7.1142
7.0384
7.0112
3.8923
MeO
O
O
37e
0.93
0.89
2.87
0.93
1.03
1.86
3.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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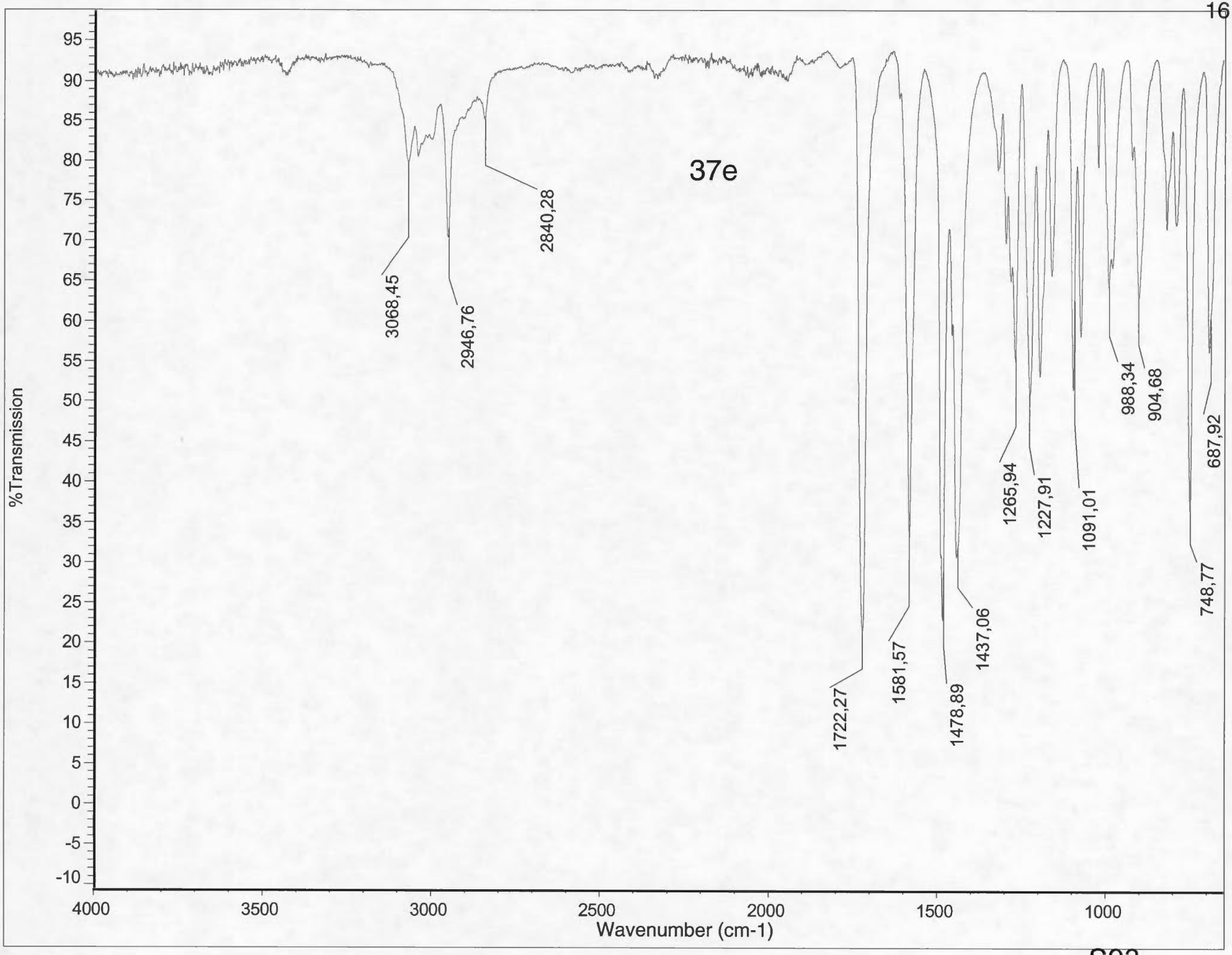
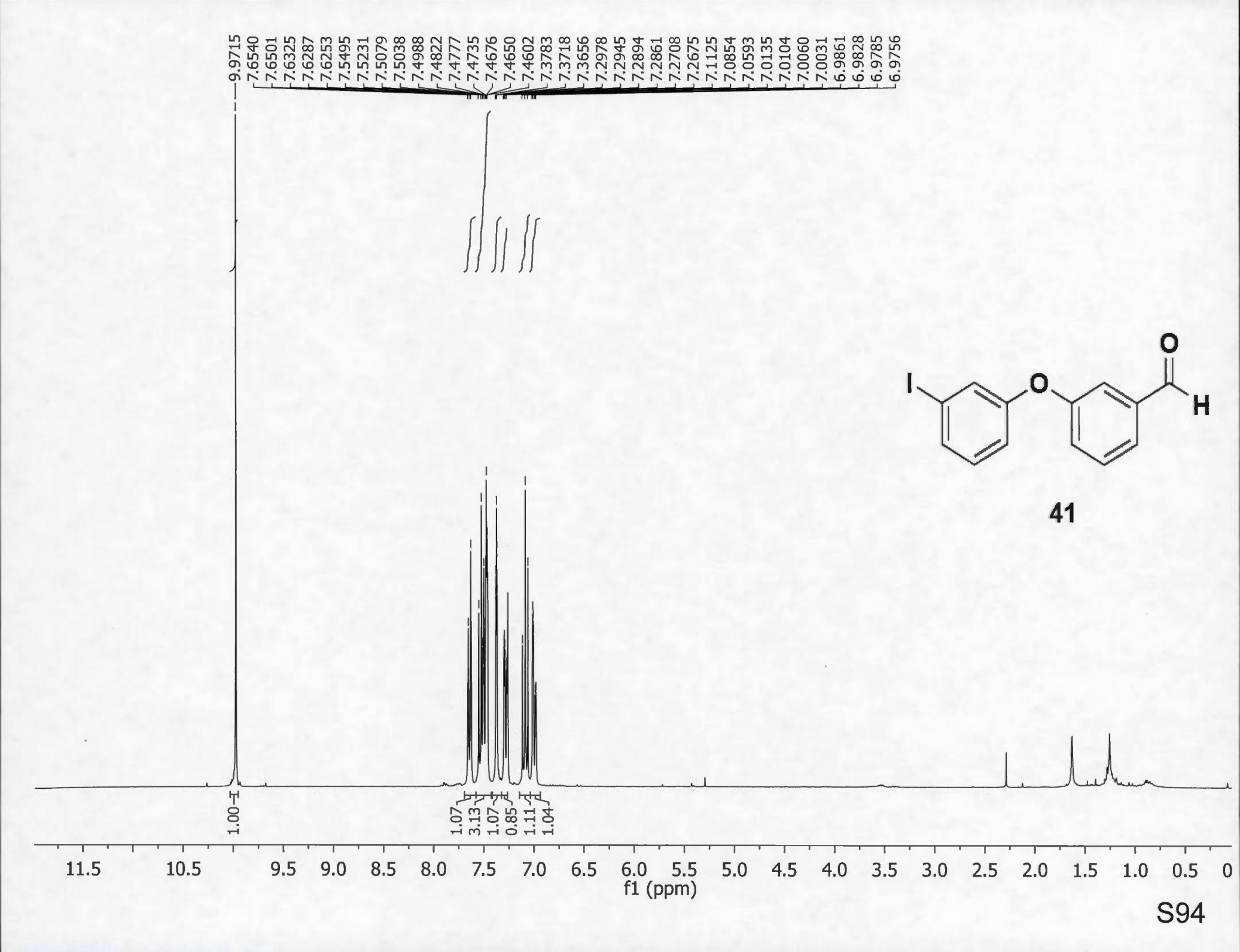
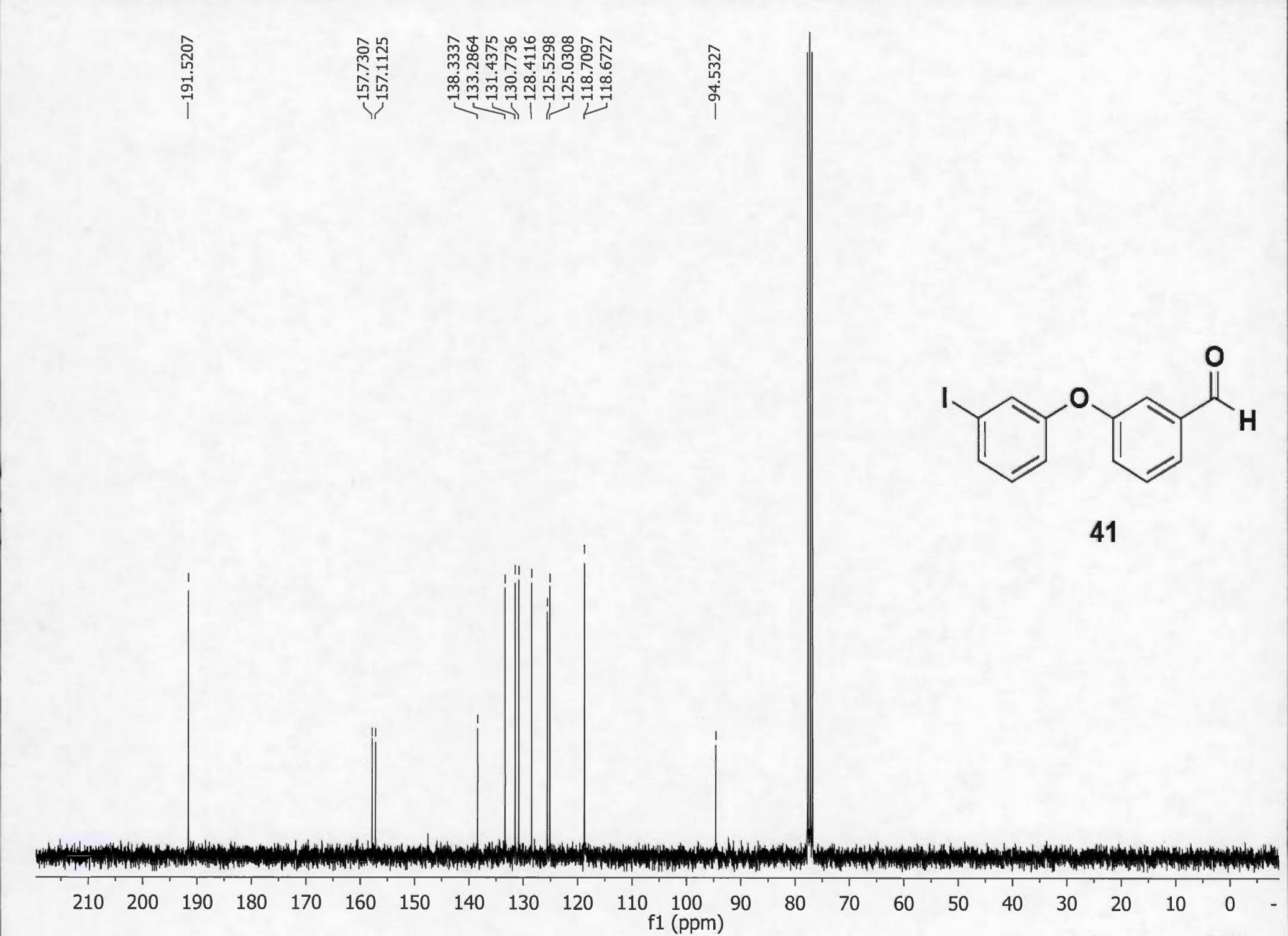
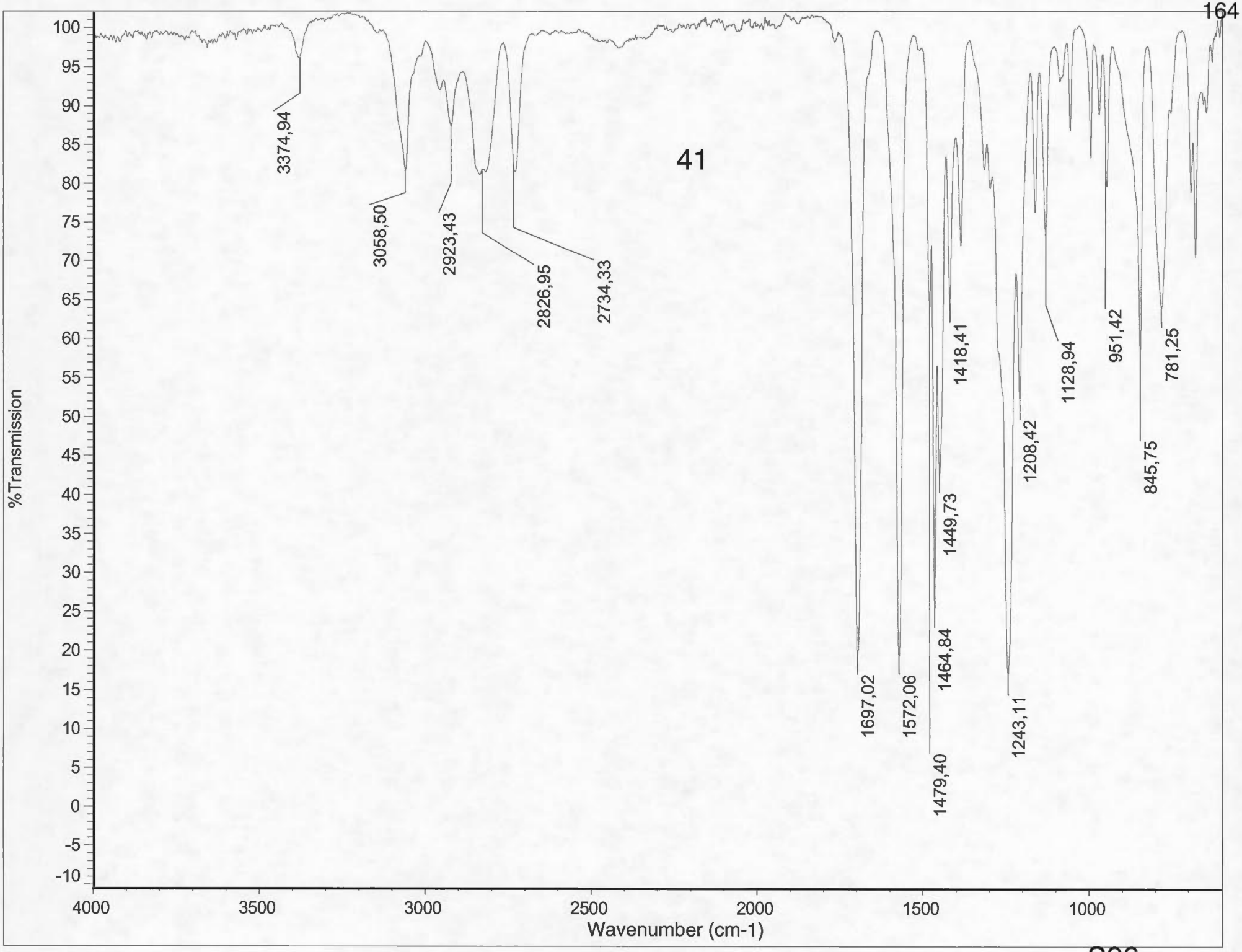
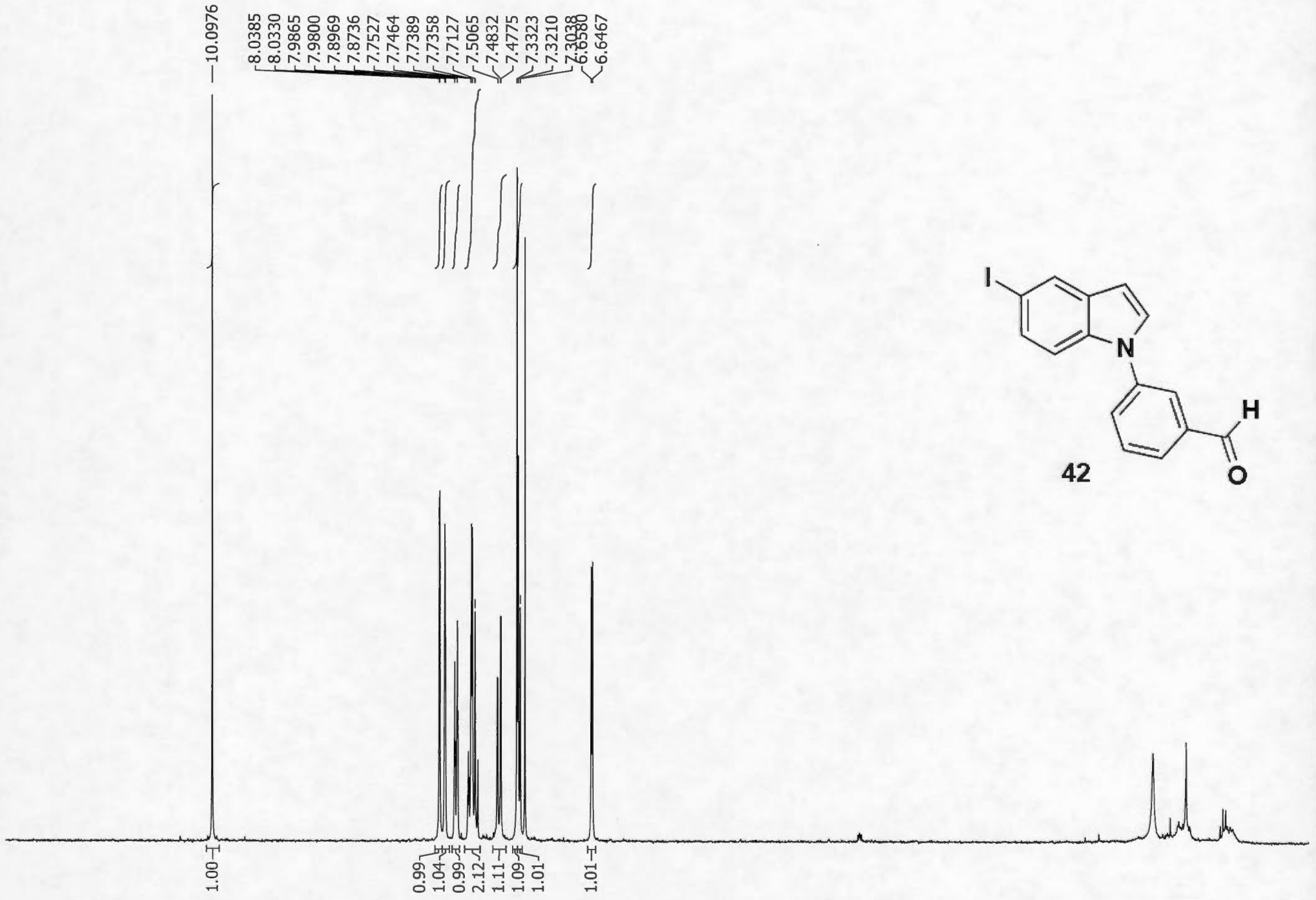
157.4845
156.7299
131.9445
129.9386
129.7721
124.3238
123.7569
123.3210
119.5764
119.1084
52.2280
MeO
O
O
37e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


37e
%Transmission
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
4000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)
3068,45
2946,76
2840,28
1722,27
1581,57
1478,89
1437,06
1265,94
1227,91
1091,01
988,34
904,68
748,77
687,92


9.9715
7.6540
7.6501
7.6325
7.6287
7.6253
7.5495
7.5231
7.5079
7.5038
7.4988
7.4822
7.4777
7.4735
7.4676
7.4650
7.4602
7.3783
7.3718
7.3656
7.2978
7.2945
7.2894
7.2861
7.2708
7.2675
7.1125
7.0854
7.0593
7.0135
7.0104
7.0060
7.0031
6.9861
6.9828
6.9785
6.9756
1.00
1.07
3.13
1.07
0.85
1.11
1.04
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)
I
O
O
H
41


191.5207
157.7307
157.1125
138.3337
133.2864
131.4375
130.7736
128.4116
125.5298
125.0308
118.7097
118.6727
94.5327
I
O
O
H
41
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -
f1 (ppm)


41
%Transmission
Wavenumber (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
4000
3500
3000
2500
2000
1500
1000
3374,94
3058,50
2923,43
2826,95
2734,33
1697,02
1572,06
1479,40
1464,84
1449,73
1418,41
1243,11
1208,42
1128,94
951,42
845,75
781,25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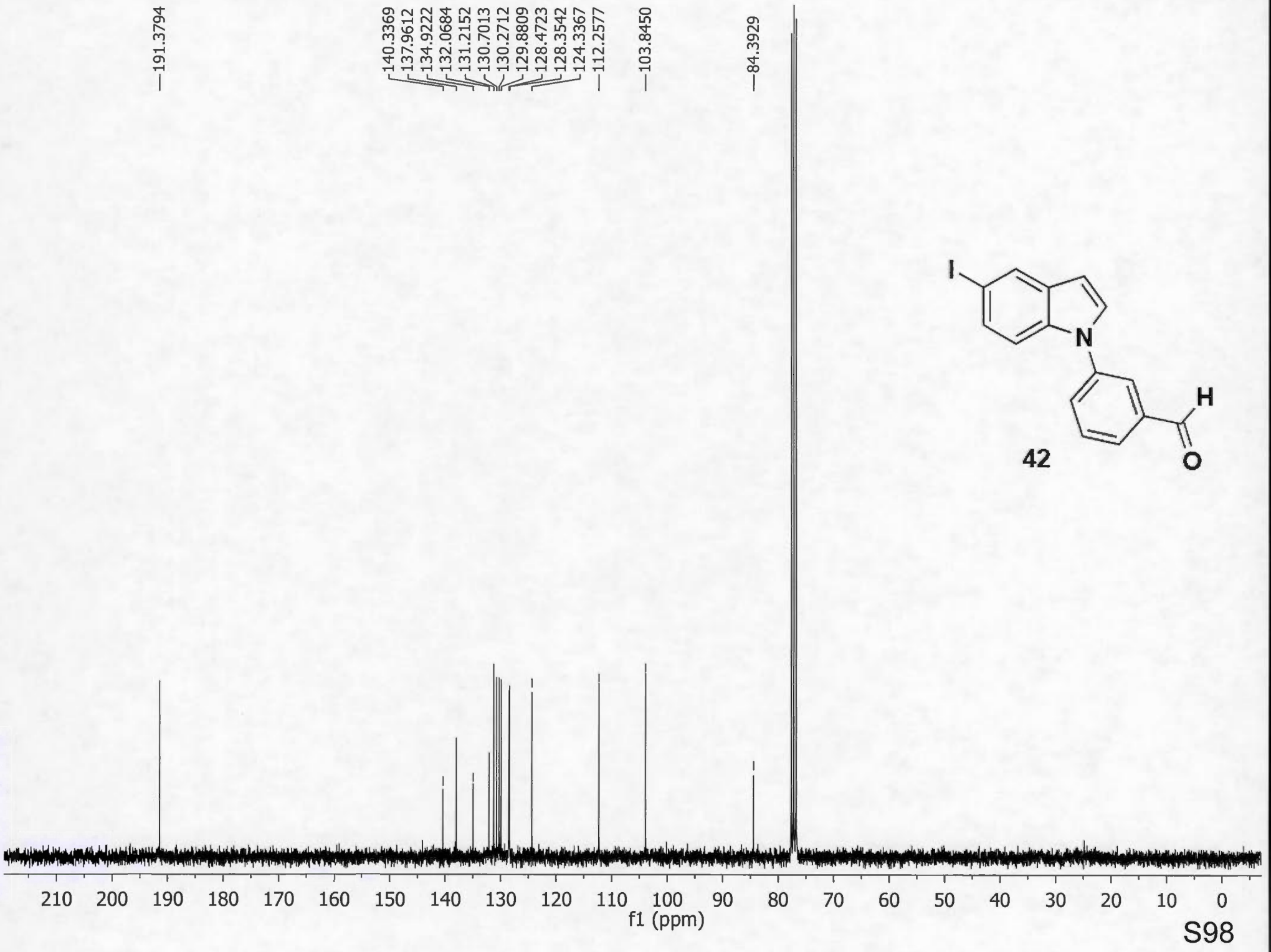
8.0330
7.9865
7.9800
7.8969
7.8736
7.7527
7.7464
7.7389
7.7358
7.7127
7.5065
7.4832
7.4775
7.3323
7.3210
7.3038
6.6580
6.6467
1.00
0.99
1.04
0.99
2.12
1.11
1.09
1.01
1.01
I
N
H
O
42
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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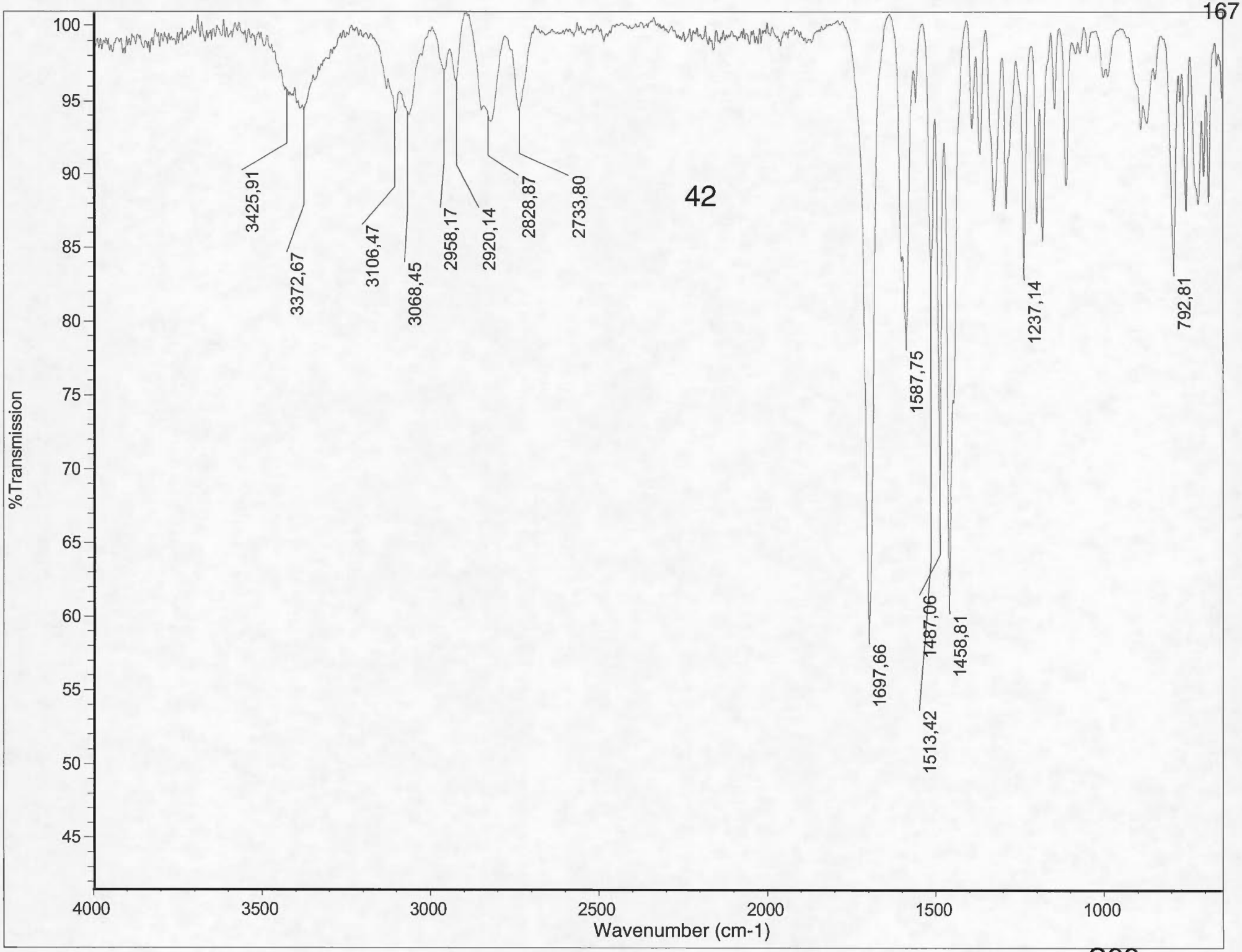
137.9612
134.9222
132.0684
131.2152
130.7013
130.2712
129.8809
128.4723
128.3542
124.3367
112.2577
103.8450
84.3929
I
N
H
O
42
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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Wavenumber (cm-1)
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90
85
80
75
70
65
60
55
50
45
4000
3500
3000
2500
2000
1500
1000
3425,91
3372,67
3106,47
3068,45
2958,17
2920,14
2828,87
2733,80
1697,66
1587,75
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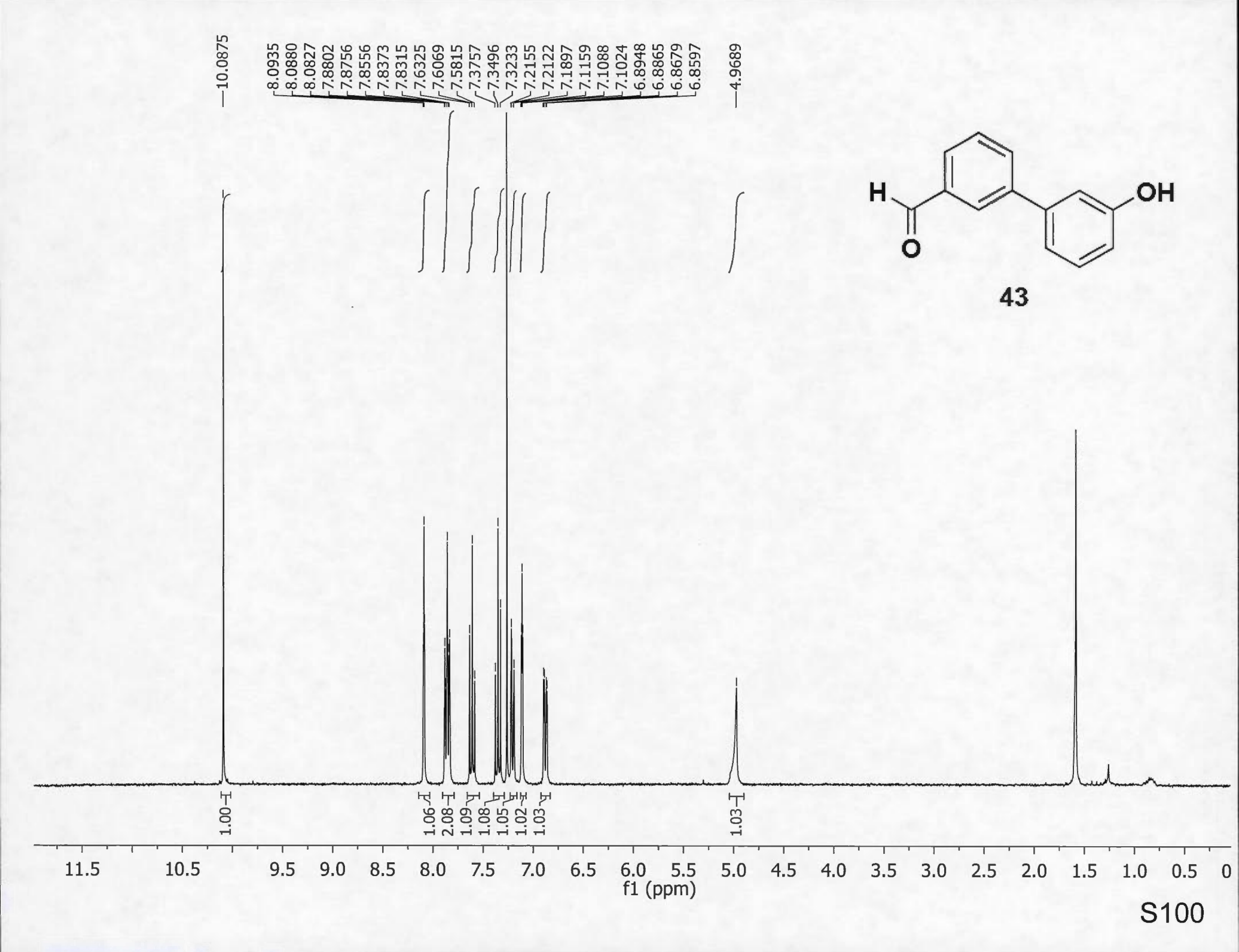
1487,06
1458,81
1237,14
792,81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8.0827
7.8802
7.8756
7.8556
7.8373
7.8315
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7.6069
7.5815
7.3757
7.3496
7.3233
7.2155
7.2122
7.1897
7.1159
7.1088
7.1024
6.8948
6.8865
6.8679
6.8597
4.9689
H
O
OH
43
1.00
1.06
2.08
1.09
1.08
1.05
1.02
1.03
1.03
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
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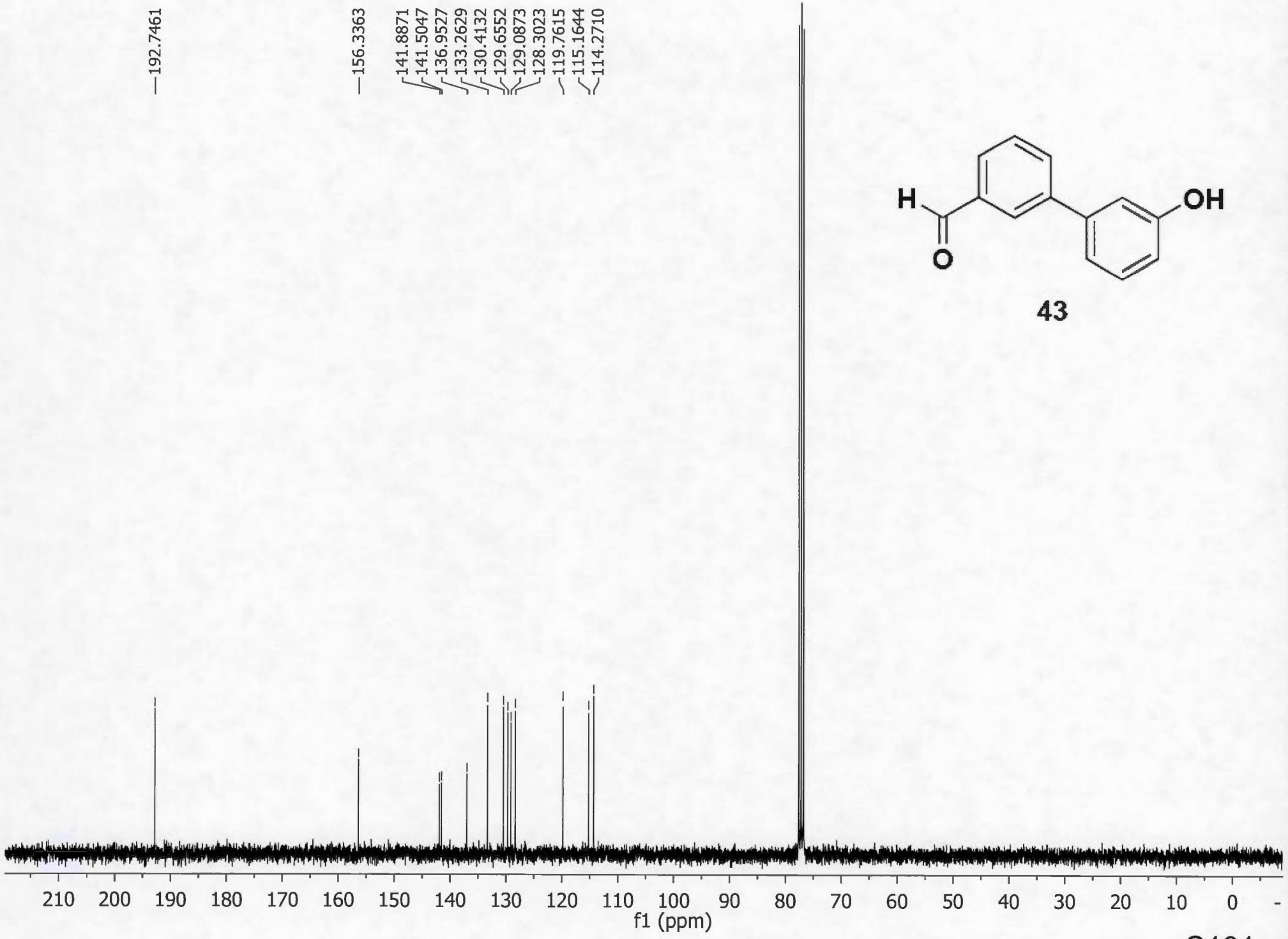
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)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141.5047
136.9527
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130.4132
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129.0873
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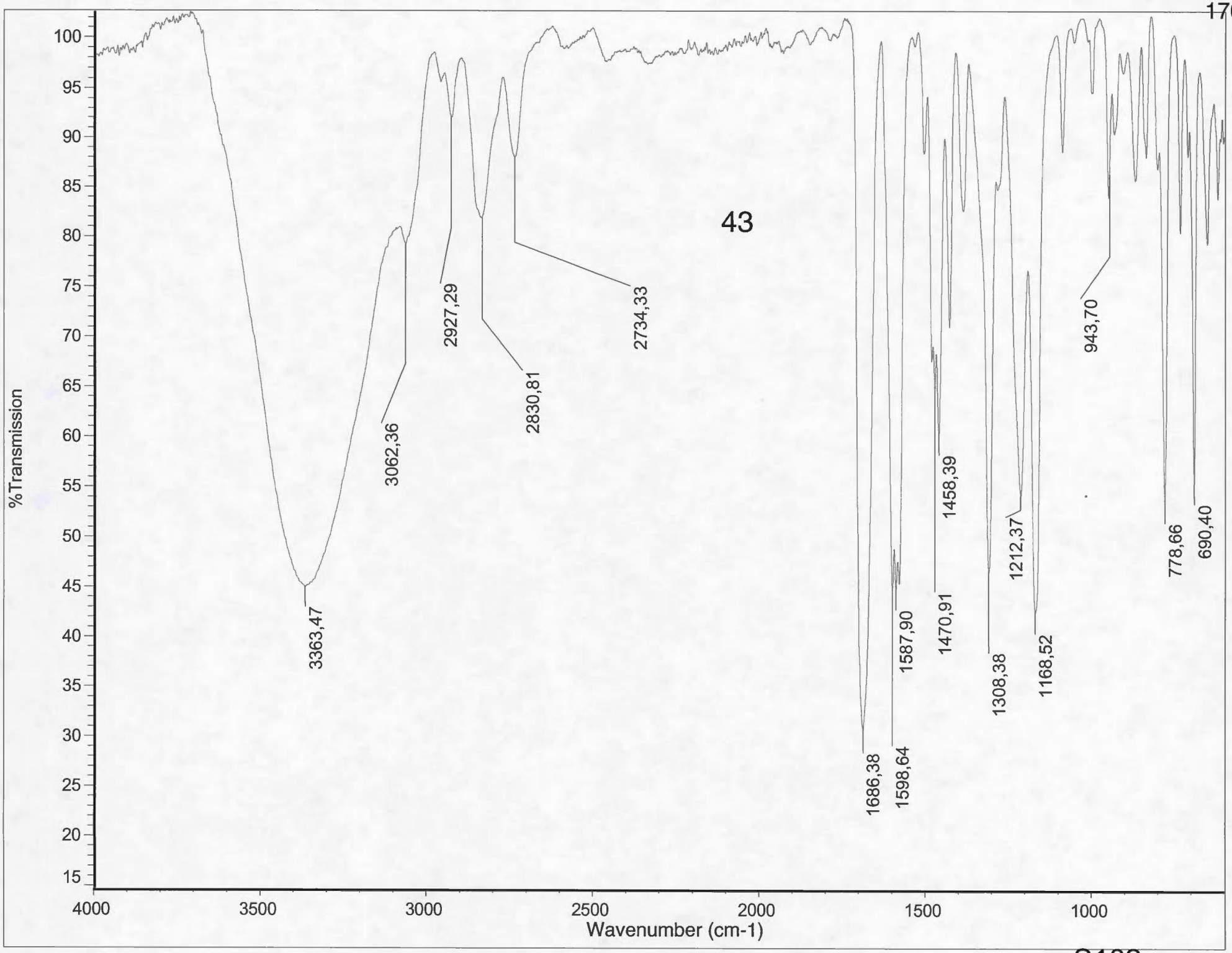
115.1644
114.2710
H
O
OH
43
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -
f1 (ppm)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%Transmission
Wavenumber (cm-1)
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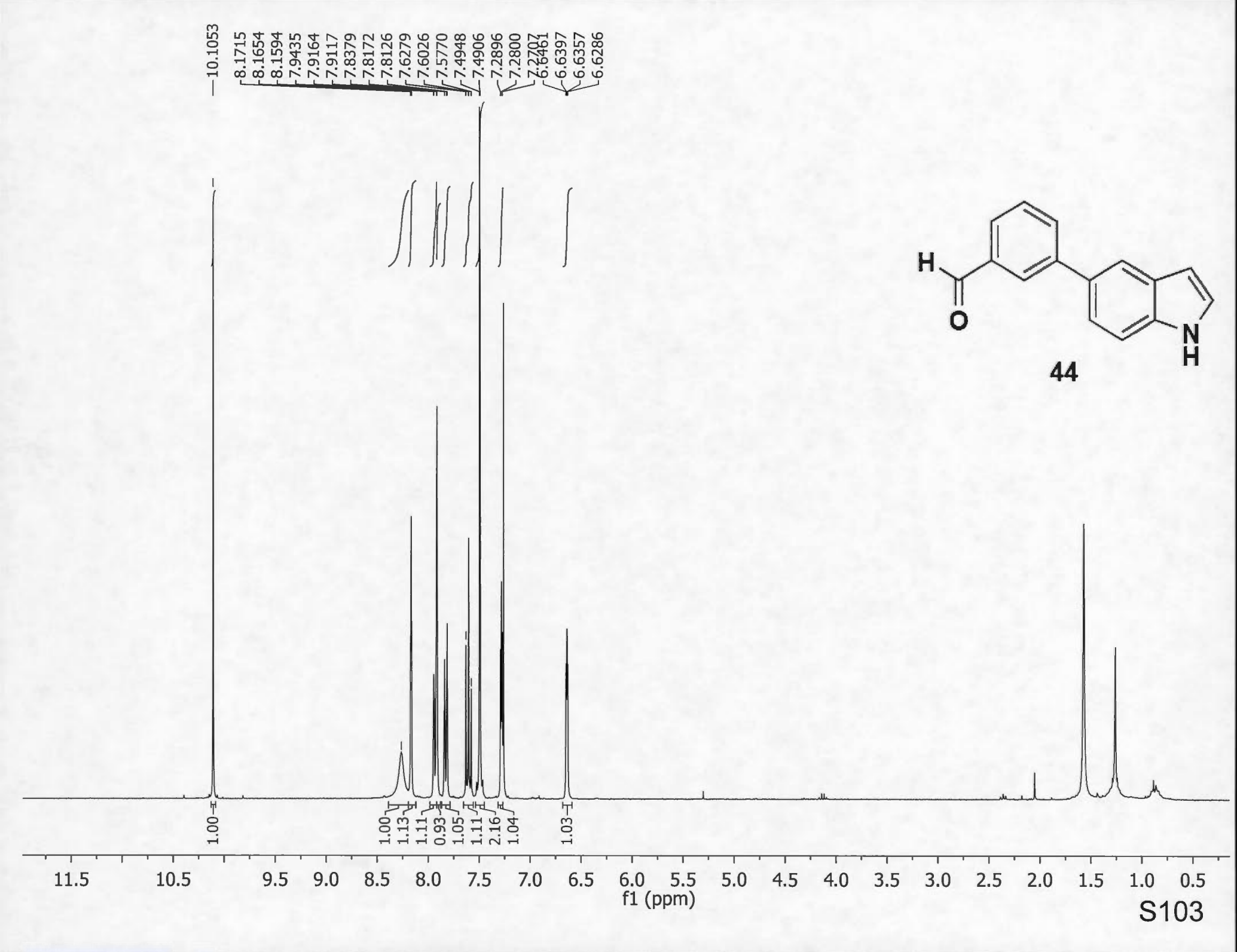
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
3363,47
3062,36
2927,29
2830,81
2734,33
1686,38
1598,64
1587,90
1470,91
1458,39
1308,38
1212,37
1168,52
943,70
778,66
690,40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8.1594
7.9435
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7.8172
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7.6026
7.5770
7.4948
7.4906
7.2896
7.2800
7.2707
6.6461
6.6397
6.6357
6.6286
1.00
1.00
1.13
1.11
0.93
1.05
1.11
2.16
1.04
1.03
H
O
N
H
44
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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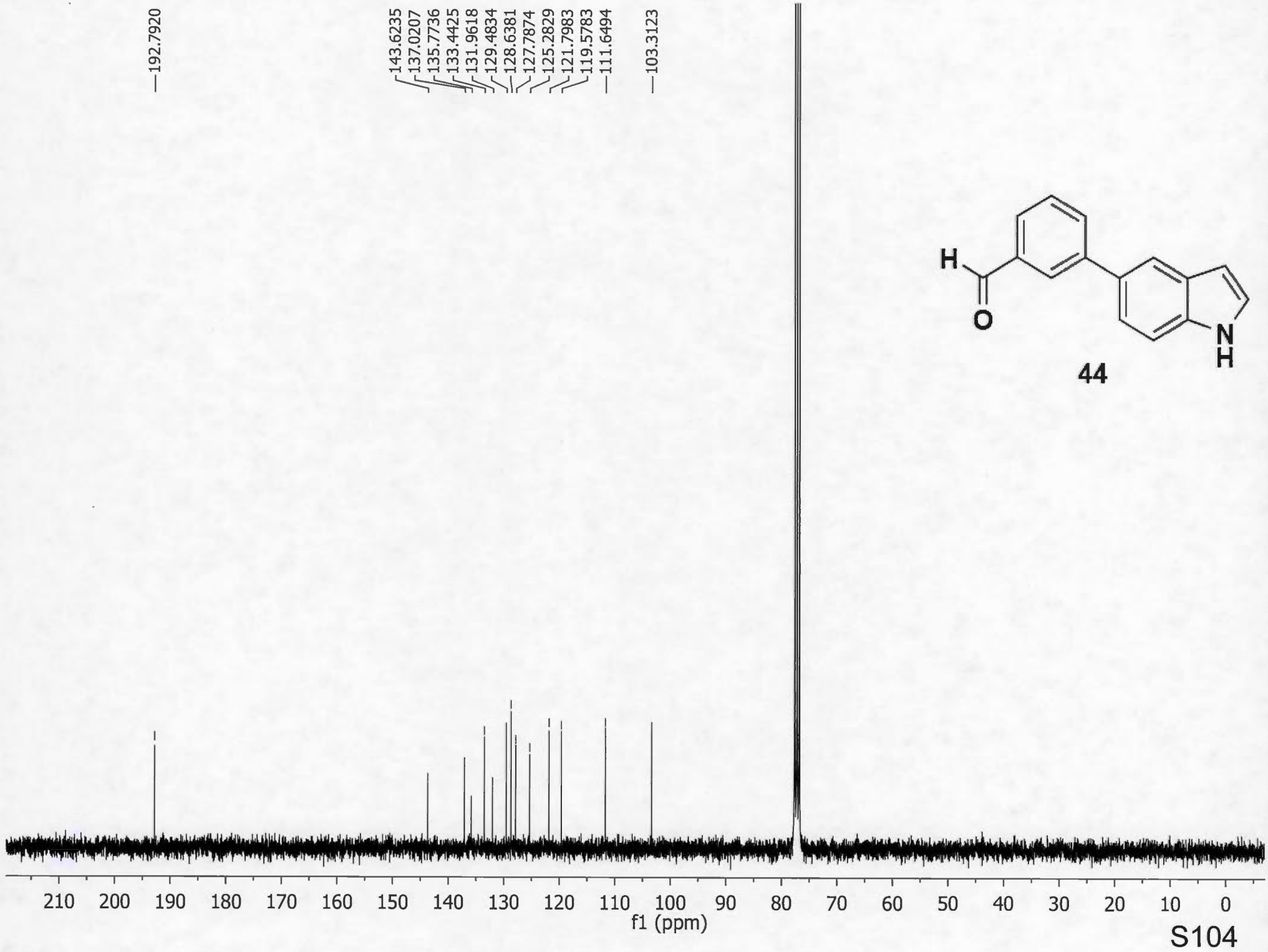
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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119.5783
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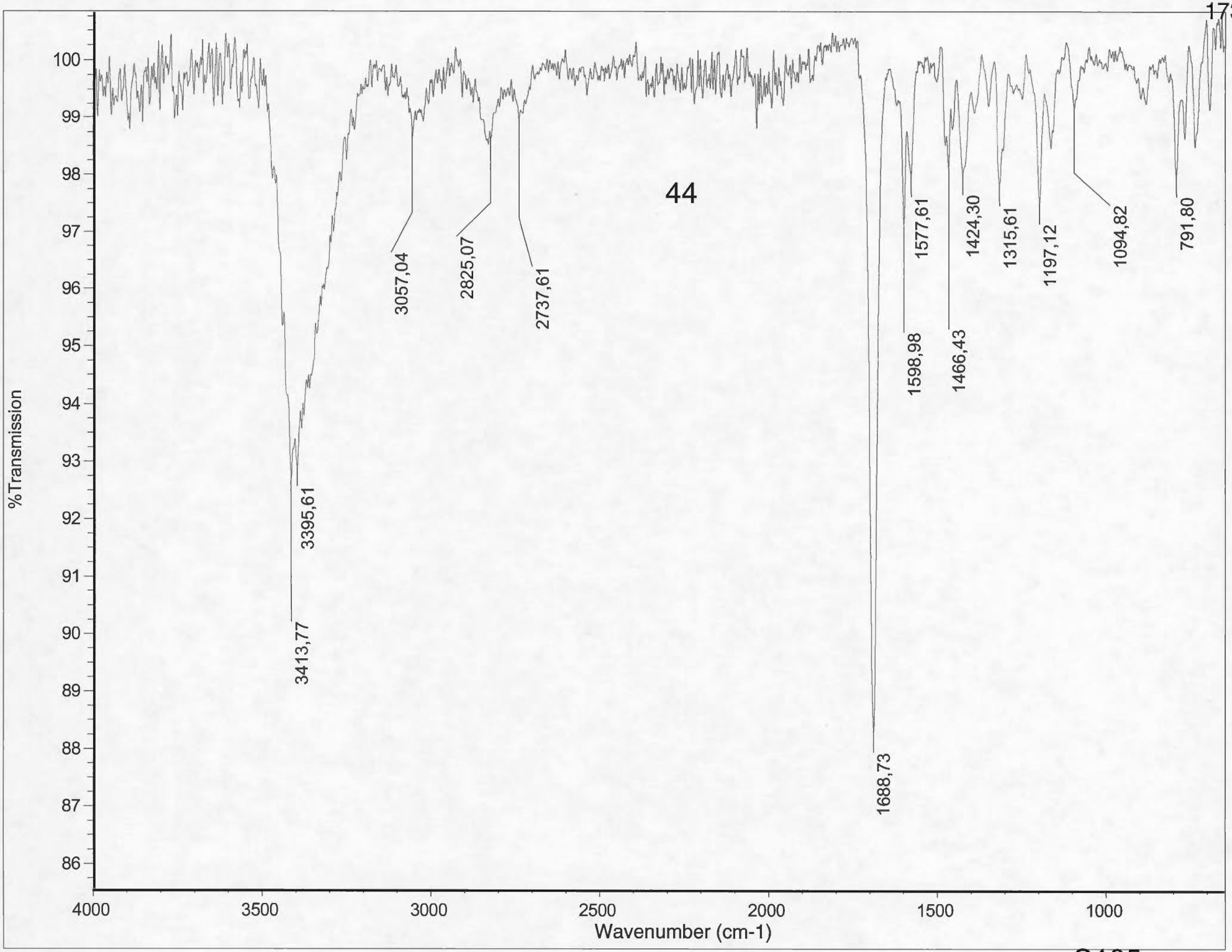
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


44
%Transmission
Wavenumber (cm-1)
100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
4000
3500
3000
2500
2000
1500
1000
3413,77
3395,61
3057,04
2825,07
2737,61
1688,73
1598,98
1577,61
1466,43
1424,30
1315,61
1197,12
1094,82
791,80

Crystallographic analysis

Single-crystal X-ray diffraction data were acquired at the Mo *Kα* or Cu *Kα* wavelength. The structure for **21b** was reported previously (CCDC code 949485).[i]

Tris(3-cyclopropylphenyl)bismuthine (1f)

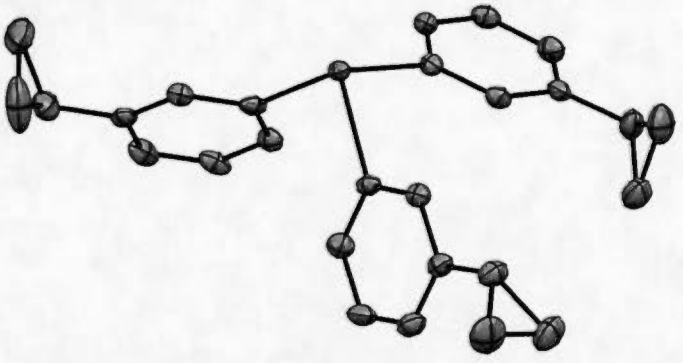


Figure S1. ORTEP view at 50% ellipsoid probability for compound **1f.**

A colorless plate-like specimen of $C_{27}H_{27}Bi$, approximate dimensions 0.058 mm x 0.146 mm x 0.267 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1464 frames were collected. The total exposure time was 4.07 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 24743 reflections to a maximum θ angle of 27.65° (0.77 Å resolution), of which 5061 were independent (average redundancy 4.889, completeness = 99.7%, R_{int} = 5.73%, R_{sig} = 4.73%) and 4135 (81.70%) were greater than $2\sigma(F^2)$. The final cell constants of a = 17.2733(15) Å, b = 6.1956(5) Å, c = 20.4121(18) Å, β = 92.6470(10)°, volume = 2182.1(3) Å^3, are based upon the refinement of the XYZ-centroids of 7035 reflections above 20 σ(I) with 4.721° < 2θ < 52.57°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.648. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.4835 and 0.7456. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/n 1, with Z = 4 for the formula unit, $C_{27}H_{27}Bi$. The final anisotropic full-matrix least-squares refinement on F^2 with 253 variables converged at R1 = 2.58%, for the observed data and wR2 = 5.06% for all data. The goodness-of-fit was 1.016. The largest peak in the final difference electron density synthesis was 0.659 e$^-$/Å^3 and the largest hole was -0.848 e$^-$/Å^3 with an RMS deviation of 0.129 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.706 g/cm^3 and F(000), 1088 e$^-$.

[i] Petiot, P.; Gagnon, A. *Eur. J. Org. Chem.* **2013**, 5282-5289.

Tris(3,5-difluorophenyl)bismuthine (1i)

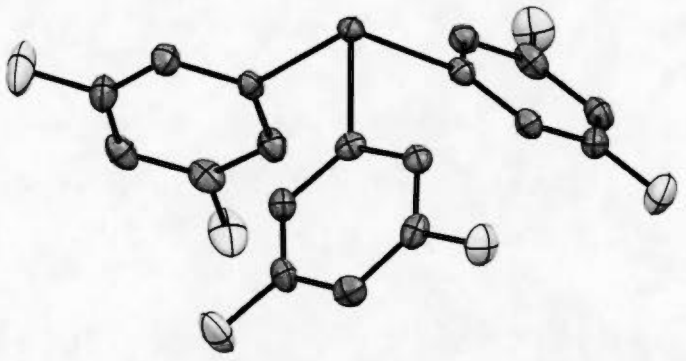


Figure S2. ORTEP view at 50% ellipsoid probability for compound **1i.**

A colorless plate-like specimen of $C_{18}H_9BiF_6$, approximate dimensions 0.055 mm x 0.122 mm x 0.189 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 5856 frames were collected. The total exposure time was 8.13 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 22071 reflections to a maximum θ angle of 68.28° (0.83 Å resolution), of which 2867 were independent (average redundancy 7.698, completeness = 98.6%, R_{int} = 4.33%, R_{sig} = 2.53%) and 2746 (95.78%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 5.16200(10) Å, $\underline{b}$ = 15.7296(3) Å, $\underline{c}$ = 19.6908(3) Å, β = 97.0350(10)°, volume = 1586.78(5) Å^3, are based upon the refinement of the XYZ-centroids of 9954 reflections above 20 σ(I) with 7.214° < 2θ < 136.4°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.523. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.3941 and 0.7531. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with Z = 4 for the formula unit, $C_{18}H_9BiF_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 226 variables converged at R1 = 1.89%, for the observed data and wR2 = 4.92% for all data. The goodness-of-fit was 1.088. The largest peak in the final difference electron density synthesis was 0.564 e^-/Å^3 and the largest hole was -0.898 e^-/Å^3 with an RMS deviation of 0.111 e^-/Å^3. On the basis of the final model, the calculated density was 2.295 g/cm^3 and F(000), 1016 e^-.

Tris(4-methoxyphenyl)bismuthine (1k)

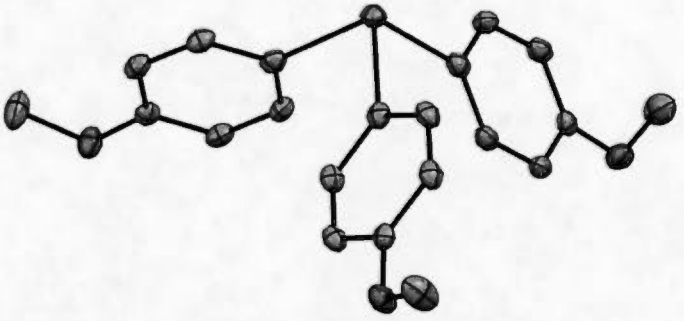


Figure S3. ORTEP view at 50% ellipsoid probability for compound **1k.**

A colorless rhomb-like specimen of $C_{21}H_{21}BiO_3$, approximate dimensions 0.204 mm x 0.395 mm x 0.417 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1464 frames were collected. The total exposure time was 0.41 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a trigonal unit cell yielded a total of 11061 reflections to a maximum θ angle of 27.53° (0.77 Å resolution), of which 1424 were independent (average redundancy 7.768, completeness = 99.9%, R_{int} = 5.08%, R_{sig} = 2.50%) and 1356 (95.22%) were greater than $2\sigma(F^2)$. The final cell constants of a = 13.0227(11) Å, b = 13.0227(11) Å, c = 18.9137(13) Å, volume = 2777.9(5) Å^3, are based upon the refinement of the XYZ-centroids of 5605 reflections above 20 σ(I) with 5.617° < 2θ < 54.88°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.683. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.5092 and 0.7456. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group R -3, with Z = 6 for the formula unit, $C_{21}H_{21}BiO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 77 variables converged at R1 = 1.80%, for the observed data and wR2 = 3.81% for all data. The goodness-of-fit was 1.103. The largest peak in the final difference electron density synthesis was 0.575 $e^-/Å^3$ and the largest hole was -0.819 $e^-/Å^3$ with an RMS deviation of 0.091 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.902 g/cm^3 and F(000), 1524 e^-.

Tris(2-(diethoxymethyl)phenyl)bismuthine (1n)

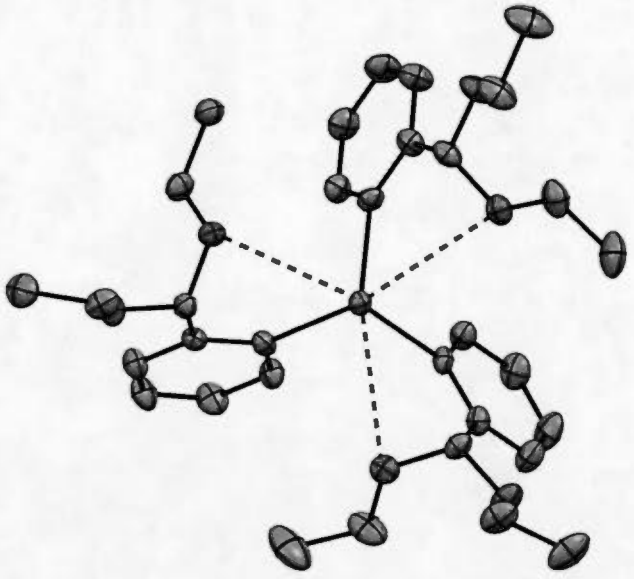


Figure S4. ORTEP view at 50% ellipsoid probability for compound **1n.**

A colorless plate-like specimen of $C_{33}H_{45}BiO_6$, approximate dimensions 0.039 mm x 0.067 mm x 0.220 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 5856 frames were collected. The total exposure time was 6.30 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 149815 reflections to a maximum θ angle of 68.39° (0.83 Å resolution), of which 18042 were independent (average redundancy 8.304, completeness = 99.5%, R_{int} = 6.47%, R_{sig} = 3.25%) and 13630 (75.55%) were greater than $2\sigma(F^2)$. The final cell constants of a = 12.2493(2) Å, b = 40.0209(5) Å, c = 23.2425(3) Å, β = 119.9300(10)°, volume = 9874.6(3) Å^3, are based upon the refinement of the XYZ-centroids of 9835 reflections above 20 σ(I) with 8.329° < 2θ < 136.6°. Data were corrected for absorption effects using the numerical method (SADABS). The ratio of minimum to maximum apparent transmission was 0.404. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.2896 and 0.7169. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with Z = 12 for the formula unit, $C_{33}H_{45}BiO_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 1099 variables converged at R1 = 2.67%, for the observed data and wR2 = 6.33% for all data. The goodness-of-fit was 1.004. The largest peak in the final difference electron density synthesis was 0.550 e$^-$/Å^3 and the largest hole was -1.148 e$^-$/Å^3 with an RMS deviation of 0.085 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.507 g/cm^3 and F(000), 4488 e$^-$.

3,3',3"-bismuthinetriyltribenzonitrile (1s)

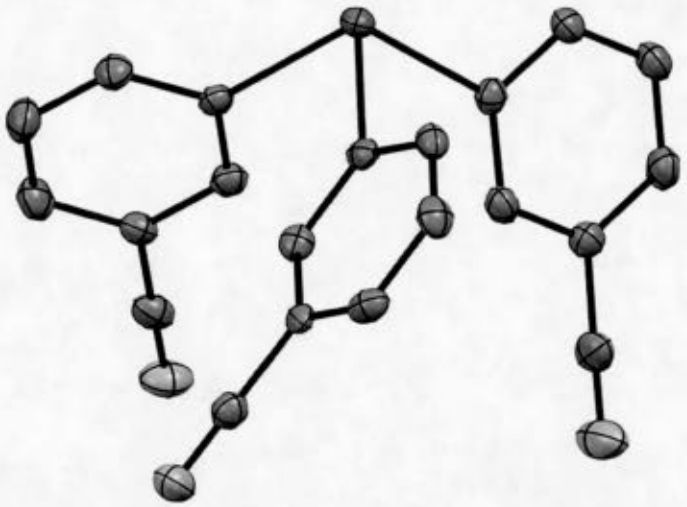


Figure S5. ORTEP view at 50% ellipsoid probability for compound **1s.**

A clear colorless block-like specimen of $C_{21}H_{12}BiN_3$, approximate dimensions 0.142 mm x 0.330 mm x 0.532 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1464 frames were collected. The total exposure time was 0.41 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 20762 reflections to a maximum θ angle of 27.50° (0.77 Å resolution), of which 4081 were independent (average redundancy 5.087, completeness = 99.6%, R_{int} = 5.36%, R_{sig} = 3.99%) and 3398 (83.26%) were greater than $2\sigma(F^2)$. The final cell constants of a = 8.5793(8) Å, b = 11.6696(11) Å, c = 17.9621(16) Å, β = 96.1690(10)°, volume = 1787.9(3) $Å^3$, are based upon the refinement of the XYZ-centroids of 6528 reflections above 20 σ(I) with 4.775° < 2θ < 54.58°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.494. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.3684 and 0.7456. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with Z = 4 for the formula unit, $C_{21}H_{12}BiN_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 226 variables converged at R1 = 2.25%, for the observed data and wR2 = 4.67% for all data. The goodness-of-fit was 1.017. The largest peak in the final difference electron density synthesis was 0.501 $e^-/Å^3$ and the largest hole was -0.842 $e^-/Å^3$ with an RMS deviation of 0.120 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.914 g/cm^3 and F(000), 968 e^-.

Trimethyl 4,4',4"-bismuthinetriyltribenzoate (1t)

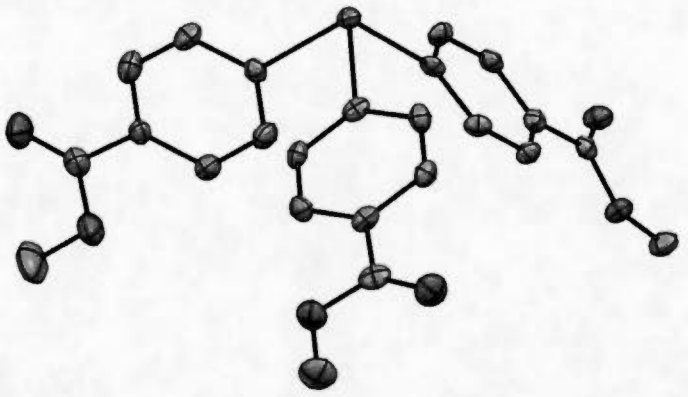


Figure S6. ORTEP view at 50% ellipsoid probability for compound **1t.**

A clear colorless plate-like specimen of $C_{24}H_{21}BiO_6$, approximate dimensions 0.038 mm x 0.266 mm x 0.307 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1464 frames were collected. The total exposure time was 4.07 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 12705 reflections to a maximum θ angle of 27.80° (0.76 Å resolution), of which 5155 were independent (average redundancy 2.465, completeness = 97.5%, R_{int} = 5.08%, R_{sig} = 6.80%) and 4499 (87.27%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 5.7360(7) Å, $\underline{b}$ = 10.0706(12) Å, $\underline{c}$ = 19.648(2) Å, α = 96.3650(10)°, β = 90.7050(10)°, γ = 98.8130(10)°, volume = 1114.2(2) Å^3, are based upon the refinement of the XYZ-centroids of 5695 reflections above 20 σ(I) with 5.520° < 2θ < 53.85°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.611. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.4554 and 0.7456. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z = 2 for the formula unit, $C_{24}H_{21}BiO_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 283 variables converged at R1 = 3.64%, for the observed data and wR2 = 8.12% for all data. The goodness-of-fit was 1.060. The largest peak in the final difference electron density synthesis was 1.828 e^-/Å^3 and the largest hole was -1.530 e^-/Å^3 with an RMS deviation of 0.175 e^-/Å^3. On the basis of the final model, the calculated density was 1.831 g/cm^3 and F(000), 592 e^-.

Tris(2-formylphenyl)bismuthine (21c)

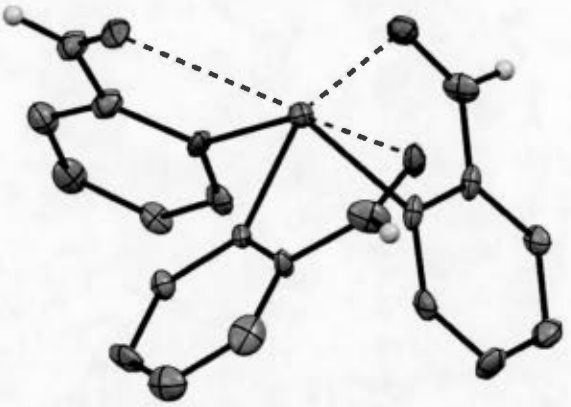


Figure S7. ORTEP view at 50% ellipsoid probability for compound **21c.**

A plate-like specimen of $C_{21}H_{15}BiO_3$, approximate dimensions 0.053 mm x 0.104 mm x 0.147 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The total exposure time was 4.07 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 15775 reflections to a maximum θ angle of 27.51° (0.77 Å resolution), of which 5124 were independent (average redundancy 3.08, completeness = 99.9%, R_{int} = 7.17%, R_{sig} = 6.93%) and 3198 (62.41%) were greater than $2\sigma(F^2)$. The final cell constants of a = 5.3061(7) Å, b = 16.256(2) Å, c = 10.1005(16) Å, β = 98.294(2)°, volume = 862.1(2) Å^3, are based upon the refinement of the XYZ-centroids of 3696 reflections above 20 σ(I) with 4.783° < 2θ < 54.03°. Data were corrected for absorption effects using TWINABS. The ratio of minimum to maximum apparent transmission was 0.730. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.4831 and 0.7456. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 c 1, with Z = 2 for the formula unit, $C_{21}H_{15}BiO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 215 variables converged at R1 = 3.61%, for the observed data and wR2 = 9.93% for all data. The goodness-of-fit was 1.048. The largest peak in the final difference electron density synthesis was 1.284 e^-/Å^3 and the largest hole was -1.685 e^-/Å^3 with an RMS deviation of 0.198 e^-/Å^3. On the basis of the final model, the calculated density was 2.020 g/cm^3 and F(000), 496 e^-.

Tris(3-(hydroxymethyl)phenyl)bismuthine (21e)

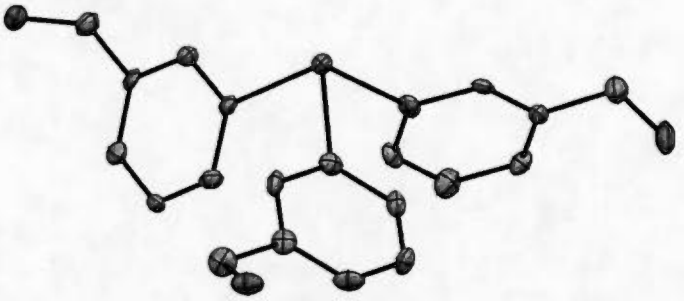


Figure S8. ORTEP view at 50% ellipsoid probability for compound **21e.**

A colorless rhomb-like specimen of $C_{21}H_{21}BiO_3$, approximate dimensions 0.045 mm x 0.054 mm x 0.140 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1464 frames were collected. The total exposure time was 4.07 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 20965 reflections to a maximum θ angle of 27.63° (0.77 Å resolution), of which 4213 were independent (average redundancy 4.976, completeness = 99.0%, R_{int} = 8.70%, R_{sig} = 6.72%) and 3219 (76.41%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 25.024(2) Å, $\underline{b}$ = 6.1831(6) Å, $\underline{c}$ = 23.770(2) Å, β = 94.7380(10)°, volume = 3665.3(6) Å^3, are based upon the refinement of the XYZ-centroids of 3217 reflections above 20 σ(I) with 4.935° < 2θ < 45.59°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.702. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.5231 and 0.7456. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group C 1 2/c 1, with Z = 8 for the formula unit, $C_{21}H_{21}BiO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 235 variables converged at R1 = 3.35%, for the observed data and wR2 = 7.22% for all data. The goodness-of-fit was 1.015. The largest peak in the final difference electron density synthesis was 0.819 e^-/Å^3 and the largest hole was -1.464 e^-/Å^3 with an RMS deviation of 0.191 e^-/Å^3. On the basis of the final model, the calculated density was 1.922 g/cm^3 and F(000), 2032 e^-.

(*E*)-Ethyl 3-(3-(3-cyano-2-oxopyridin-1(*2H*)-yl)phenyl)acrylate (17a)

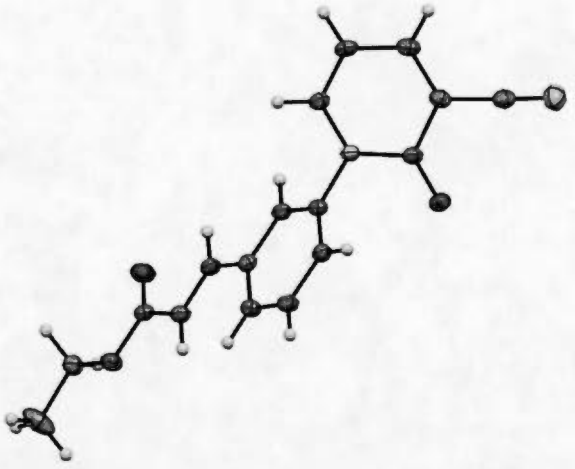


Figure S9. ORTEP view at 50% ellipsoid probability for compound **17a.**

A colorless plate-like specimen of $C_{17}H_{14}N_2O_3$, approximate dimensions 0.028 mm x 0.139 mm x 0.546 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 5856 frames were collected. The total exposure time was 10.47 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 14337 reflections to a maximum θ angle of 68.31° (0.83 Å resolution), of which 4311 were independent (average redundancy 3.326, completeness = 98.8%, R_{int} = 6.23%, R_{sig} = 4.18%) and 3773 (87.52%) were greater than $2\sigma(F^2)$. The final cell constants of a = 7.0152(3) Å, b = 7.0736(4) Å, c = 15.1206(8) Å, α = 83.644(3)°, β = 80.150(3)°, γ = 73.302(3)°, volume = 706.58(6) Å^3, are based upon the refinement of the XYZ-centroids of 4294 reflections above 20 σ(I) with 5.942° < 2θ < 136.3°. Data were corrected for absorption effects using TWINABS. The ratio of minimum to maximum apparent transmission was 0.857. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.5767 and 0.7531. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z = 2 for the formula unit, $C_{17}H_{14}N_2O_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 202 variables converged at R1 = 4.72%, for the observed data and wR2 = 13.54% for all data. The goodness-of-fit was 1.090. The largest peak in the final difference electron density synthesis was 0.219 e$^-$/Å^3 and the largest hole was -0.196 e$^-$/Å^3 with an RMS deviation of 0.046 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.383 g/cm^3 and F(000), 308 e$^-$.

Table S1. Crystal and solution data for **1f**, **1i**, **1k**, **1n**, **1s**, **1t**, **21c**, **21e** and **17a**.

Name	**1f**	**1i**	**1k**	**1n**	**1s**
CCDC deposition number	1470682	1470683	1470684	1470685	1470686
Chemical formula	$C_{27}H_{27}Bi$	$C_{18}H_9BiF_6$	$C_{21}H_{21}BiO_3$	$C_{33}H_{45}BiO_6$	$C_{21}H_{12}BiN_3$
Formula weight (g/mol)	560.46	548.23	530.36	746.67	515.32
Temperature (K)	150(2)	150(2)	150(2)	150(2)	150(2)
Wavelength (Å)	0.71073	1.54178	0.71073	1.54178	0.71073
Crystal size (mm)	0.058 x 0.146 x 0.267	0.055 x 0.122 x 0.189	0.204 x 0.395 x 0.417	0.039 x 0.067 x 0.220	0.142 x 0.330 x 0.532
Crystal system	monoclinic	monoclinic	trigonal	monoclinic	monoclinic
Space group	P $2_1/n$	P $2_1/c$	R -3	P $2_1/c$	P $2_1/c$
a (Å)	17.2733(15)	5.16200(10)	13.0227(11)	12.2493(2)	8.5793(8)
b (Å)	6.1956(5)	15.7296(3)	13.0227(11)	40.0209(5)	11.6696(11)
c (Å)	20.4121(18)	19.6908(3)	18.9137(13)	23.2425(3)	17.9621(16)
α (°)	90	90	90	90	90
β (°)	92.6470(10)	97.0350(10)	90	119.9300(10)	96.1690(10)
γ (°)	90	90	120	90	90
Volume (Å^3)	2182.1(3)	1586.78(5)	2777.9(5)	9874.6(3)	1787.9(3)
Z	4	4	6	12	4
Density (calculated, g/cm^3)	1.706	2.295	1.902	1.507	1.914
Absorption coefficient (mm^{-1})	8.089	22.413	9.537	10.830	9.868
F(000)	1088	1016	1524	4488	968
Theta range for data collection (°)	1.51 to 27.65	3.61 to 68.28	2.10 to 27.53	2.21 to 68.39	2.09 to 27.50
Index ranges	-22<=h<=22 -7<=k<=8 -26<=l<=26	-6<=h<=6 -18<=k<=18 -23<=l<=23	-16<=h<=16 -16<=k<=16 -24<=l<=24	-14<=h<=14 -48<=k<=48 -27<=l<=28	-11<=h<=11 -15<=k<=15 -23<=l<=23
Reflections collected	24743	22071	11061	149815	20762
Independent reflections (R_{int})	5061 (0.0573)	2867 (0.0433)	1424 (0.0508)	18042 (0.0647)	4081 (0.0536)
Coverage of independent reflections	99.7%	98.6%	99.9%	99.5%	99.6%
Max. and min. transmission	0.7456 and 0.4835	0.7531 and 0.3941	0.7456 and 0.5092	0.7169 and 0.2896	0.7456 and 0.3684
Data / restraints / parameters	5061 / 0 / 253	2867 / 0 / 226	1424 / 0 / 77	18042 / 0 / 1099	4081 / 0 / 226
Goodness-of-fit on F^2	1.016	1.088	1.103	1.004	1.017
Final R indices ($I>2\sigma(I)$)	R_1 = 0.0258 wR_2 = 0.0472	R_1 = 0.0189 wR_2 = 0.0486	R_1 = 0.0180 wR_2 = 0.0377	R_1 = 0.0267 wR_2 = 0.0565	R_1 = 0.0225 wR_2 = 0.0439
Final R indices (all data)	R_1 = 0.0387 wR_2 = 0.0506	R_1 = 0.0202 wR_2 = 0.0492	R_1 = 0.0198 wR_2 = 0.0381	R_1 = 0.0431 wR_2 = 0.0633	R_1 = 0.0321 wR_2 = 0.0467
Largest diff. peak and hole (e Å^{-3})	0.659 and -0.848	0.564 and -0.898	0.575 and -0.819	0.550 and -1.148	0.501 and -0.842
Rms deviation from mean (e Å^{-3})	0.129	0.111	0.091	0.085	0.120
Absolute structure parameter (Flack)					

Table S1 (cont'd)

Name	**1t**	**21c**	**21e**	**17a**
CCDC deposition number	1470687	1470689	1470690	1470691
Chemical formula	$C_{24}H_{21}BiO_6$	$C_{21}H_{15}BiO_3$	$C_{21}H_{21}BiO_3$	$C_{17}H_{14}N_2O_3$
Formula weight (g/mol)	614.39	524.31	530.36	294.30
Temperature (K)	150(2)	150(2)	150(2)	150(2)
Wavelength (Å)	0.71073	0.71073	0.71073	1.54178
Crystal size (mm)	0.038 x 0.266 x 0.307	0.053 x 0.104 x 0.147	0.045 x 0.054 x 0.140	0.028 x 0.139 x 0.546
Crystal system	triclinic	monoclinic	monoclinic	triclinic
Space group	P -1	P c	C 2/c	P -1
a (Å)	5.7360(7)	5.3061(7)	25.024(2)	7.0152(3)
b (Å)	10.0706(12)	16.256(2)	6.1831(6)	7.0736(4)
c (Å)	19.648(2)	10.1005(16)	23.770(2)	15.1206(8)
α (°)	96.3650(10)	90	90	83.644(3)
β (°)	90.7050(10)	98.294(2)	94.7380(10)	80.150(3)
γ (°)	98.8130(10)	90	90	73.302(3)
Volume (Å^3)	1114.2(2)	862.1(2)	3665.3(6)	706.58(6)
Z	2	2	8	2
Density (calculated, g/cm^3)	1.831	2.020	1.922	1.383
Absorption coefficient (mm^{-1})	7.949	10.242	9.637	0.791
F(000)	592	496	2032	308
Theta range for data collection (°)	2.06 to 27.80	1.25 to 27.51	1.63 to 27.63	2.97 to 68.31
Index ranges	-7<=h<=7 -12<=k<=13 -25<=l<=25	-6<=h<=6 -21<=k<=0 -13<=l<=5	-32<=h<=32 -7<=k<=8 -31<=l<=30	-8<=h<=8 -8<=k<=8 0<=l<=18
Reflections collected	12705	15775	20965	14337
Independent reflections (R_{int})	5155 (0.0508)	5124 (0.717)	4213 (0.0870)	4311 (0.623)
Coverage of independent reflections	97.5%	99.9%	99.0%	98.8%
Max. and min. transmission	0.7456 and 0.4554	0.7456 and 0.4831	0.7456 and 0.5231	0.7531 and 0.5767
Data / restraints / parameters	5155 / 0 / 283	5124 / 2 / 215	4213 / 0 / 235	4311 / 0 / 202
Goodness-of-fit on F^2	1.060	1.048	1.015	1.090
Final R indices ($I>2\sigma(I)$)	R_1 = 0.0364 wR_2 = 0.0786	R_1 = 0.0361 wR_2 = 0.0881	R_1 = 0.0335 wR_2 = 0.0644	R_1 = 0.0472 wR_2 = 0.1276
Final R indices (all data)	R_1 = 0.0455 wR_2 = 0.0812	R_1 = 0.0684 wR_2 = 0.0993	R_1 = 0.0547 wR_2 = 0.0722	R_1 = 0.0547 wR_2 = 0.1354
Largest diff. peak and hole (e Å^{-3})	1.828 and -1.530	1.284 and -1.685	0.819 and -1.464	0.219 and -0.196
Rms deviation from mean (e Å^{-3})	0.175	0.198	0.191	0.046
Absolute structure parameter (Flack)		0.07(13)		

Table S2. Bi–C bond lengths and C–Bi–C angles in **1f**, **1i**, **1k**, **1n**, **1s**, **1t**, **21c**, and **21e**.

Compound	Bi–C (Å)			C–Bi–C (°)		
1f	2.253(3)	2.254(4)	2.256(4)	92.48(13)	94.93(13)	95.72(14)
1i	2.255(3)	2.263(3)	2.264(3)	92.94(12)	93.10(12)	96.19(12)
1k*	2.251(3)			93.80(9)		
1n	2.262(4)	2.272(4)	2.273(4)	93.42(13)	93.60(13)	96.12(14)
1s	2.263(3)	2.269(3)	2.273(3)	91.77(12)	93.07(12)	98.06(12)
1t	2.255(5)	2.260(5)	2.261(5)	92.10(18)	93.32(19)	94.81(17)
21c	2.232(18)	2.315(16)	2.324(16)	91.2(6)	92.2(6)	92.4(6)
21e	2.241(6)	2.254(6)	2.264(6)	91.5(2)	94.6(2)	95.6(2)

* By symmetry, all Bi–C distances and C–Bi–C angles are equal.

ANNEXE C

Manuscript 2 : Chemoselective Copper-Catalyzed *O*-Arylation of Small Tyrosine-Containing Peptides using Functionnalized Organobismuth Reagent

Chemoselective Copper-Catalyzed *O*-Arylation of Small Tyrosine-Containing Peptides using Highly Functionalized Triarylbismuthines

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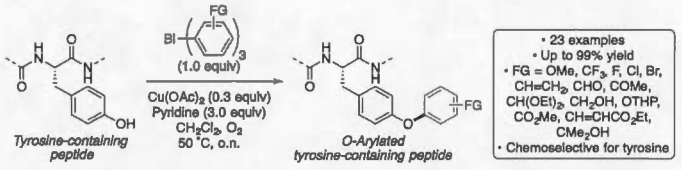
Département de chimie, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, Québec, Canada, H3C 3P8

Supporting Information Placeholder

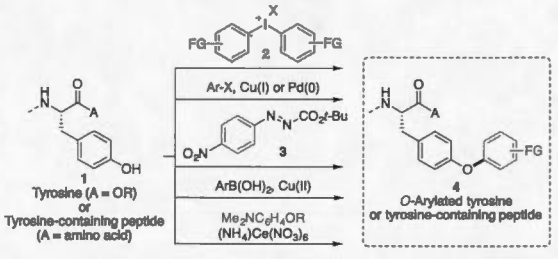


ABSTRACT: The modification of peptides is a valuable strategy to study the function of proteins and to modulate their biophysicial properties and biological activities. Tyrosine is an attractive residue for protein modification because the phenolic group has a distinct reactivity from other amino acids and because tyrosine is often present at the surface of proteins. We report herein a copper-catalyzed *O*-arylation reaction of small tyrosine-containing peptides involving highly functionalized triarylbismuthines. The reaction allows the transfer of highly functionalized aryl groups and shows excellent chemoselectivity towards tyrosine over other amino acids.

The modification of peptides by covalent bond formation has emerged as a powerful strategy to study the function of proteins.[1] Modification of single amino acids on peptides can lead to changes in conformation, biophysical properties, pharmacodynamic profile and biological activity.[2] Because of their greater accessibility, most of the protein modifications target lysines and cysteines. However, the higher reactivity of these residues can lead to reaction at multiple sites. The modification of tyrosine residues in peptides is particularly attractive since the reactivity of phenols is substantially distinct from that of functional groups contained in other amino acids. Moreover, due to their amphiphilic nature, the phenolic side chains of tyrosine are often present at the surface of proteins, making them accessible for chemical modification.

The *O*-arylation of tyrosine is an interesting strategy for peptide modification. Methods to *O*-arylate tyrosine include reaction with iodonium reagents,[3] copper[4] and palladium-catalyzed[5] coupling with aryl halides and arylation with *p*-nitro phenylazocarboxylates (**Scheme 1**).[6] To our knowledge, the *O*-arylation of tyrosine-containing peptides has only been accomplished using two approaches, namely, the oxidative coupling with *p*-dimethylaminoanisole[7] and the arylation with arylboronic acids (**Scheme 1**).[8] Other transformations that target tyrosine include the *O*-alkylation of the phenol using allylpalladium complexes,[9] reaction at the *ortho* position using Mannich-type reactions[10] and coupling with diazonium reagents.[11] However, there is still a need for *O*-arylation reaction methods that allow the chemoselective installation of highly functionalized aryl groups on tyrosine and tyrosine-containing peptides.

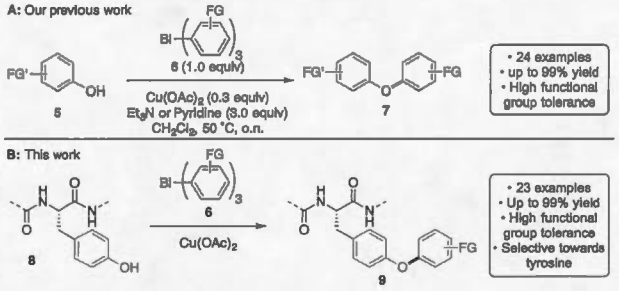
Scheme 1. Methods for the *O*-Arylation of Tyrosine and Tyrosine-Containing Peptides



Triarylbismuthines are a class of organometallic reagents that can be easily prepared from inexpensive and non-toxic bismuth salts.[12] These reagents are particularly attractive since they are air and moisture-stable, have low toxicity and show remarkable functional group tolerance. In the 1980s, Barton and Finet reported a series of seminal papers on the use of triarylbismuthines as arylating agents.[13] Triarylbismuthines have also found wide applications in the preparation of transition metal complexes,[14] in total synthesis,[15] in palladium-catalyzed cross-coupling reactions[16] and in other reactions.[17] Barton reported the *N*-arylation of unprotected amino acids esters using triphenylbismuth diacetate.[18] However, the arylation of side chains of amino acids using trivalent bismuth reagents has never been reported.

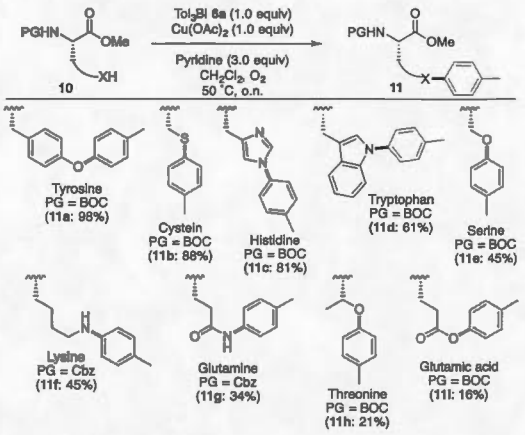
We reported over the past years a portfolio of reactions for the construction C–C,[19] C–N[20] and C–O[21] bonds involving organobismuth reagents.[22] These protocols operate under mild conditions, show high functional groups tolerance and allow the transfer of functionalized aryl and alkyl groups to medicinally relevant scaffolds. We recently demonstrated that highly functionalized diarylethers can be prepared via the copper-catalyzed *O*-arylation of phenols using triarylbismuthines (**Scheme 2A**).[21c] We report herein our studies on the copper-catalyzed *O*-arylation of tyrosine-containing peptides using triarylbismuthines (**Scheme 2B**).[23]

Scheme 2. Copper-Catalyzed Arylation of Phenols Using Triarylbismuthines and Application to the Arylation of Tyrosine-Containing Peptides



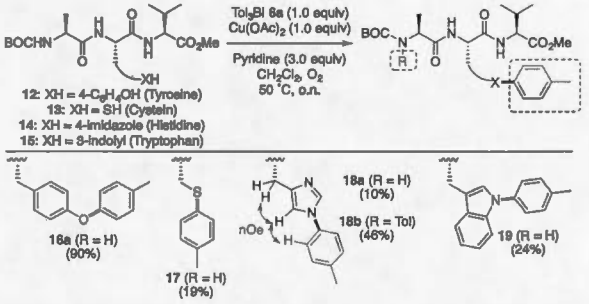
We began by evaluating the reactivity of different amino acids possessing a nucleophilic side chain under the conditions developed for the *O*-arylation of phenols (**Scheme 3**). Using 1.0 equivalent of tritolylbismuthine, 0.3 equivalents of copper acetate, and 3.0 equivalents of pyridine in dichloromethane under oxygen at 50 °C overnight, we found that tyrosine afforded the highest yield of the corresponding arylated product, followed by cystein and histidine (products **11a,b,c**). We previously demonstrated that indoles can be efficiently arylated using triarylbismuthines under copper catalysis. Here, tryptophan gave the desired *N*-tolyl derivative **11d** in 61% yield which is sligthly lower than what we observed for other simpler indoles. Serine, lysine and glutamine could also be arylated using our protocol, affording the desired arylated amino acids **11e-g** in yields ranging from 34% to 45%. Previous results from our group on the copper-catalyzed *O*-arylation of 1,2-aminoalcohols using triarylbismuthines showed that the arylation of secondary alcohols is much more challenging than primary alcohols.[20b] Therefore, as expected, threonine was arylated in a much lower yield than serine (21% for **11h** vs 45% for **11e**). Finally, glutamic acid provided the desired *O*-tolyl product **11i** in only 16% yield while aspartic acid failed to provide the desired arylation product, showing that carboxylic acids are poorly reactive under these reaction conditions. All together, these results show that while this copper-catalyzed protocol can be used to install aryl groups on the side chain of numerous amino acids, tyrosine is the most reactive amino acid.

Scheme 3. Copper-Catalyzed Arylation of Amino Acids Using Tritolylbismuthine



We then verified the reactivity of the four most reactive amino acids in the context of tripeptides. To achieve this, we prepared tripeptides where tyrosine, cysteine, histidine and tryptophan are flanked by an alanine on the *N*-terminus and a valine on the *C*-terminus and submitted them to our copper-catalyzed arylation conditions (**Scheme 4**). The results show that tyrosine retains its reactivity when incorporated in a tripeptide (**16a**). On the contrary, we found that cysteine, histidine and tryptophan lose most of their reactivity when incorporated in a tripeptide (**17**, **18a**, **19**). In the case of the histidine-containing peptide, nOe studies demonstrated that the arylation occurred at the distal nitrogen. Interestingly, a product of double arylation where a tolyl group is added at the BOC-amide was also isolated from the reaction of BOC-Ala-His-Val-OMe **18b**. These results confirm that tyrosine is the most reactive amino acid under the copper-catalyzed arylation using triarylbismuthines.

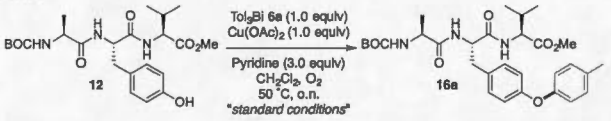
Scheme 4. Copper-Catalyzed Arylation of Tripeptides Using Tritolylbismuthine



Optimization of the reaction conditions for the tolylation of BOC-Ala-Tyr-Val-OMe **12** showed that other solvents such as toluene, acetonitrile, DMF and THF provide lower yields of the desired arylated peptide **16a** (Table 1, Entries 2-5). Use of only 1.0 equivalent of pyridine (Entry 6) or replacement by triethlyamine (Entry 7) was found to be well tolerated. Reduction of the catalyst loading to 0.3 equivalents was well tolerated also (Entry 8) but further reduction to 0.1 equivalent was detrimental to the reaction (Entry 9). It is well known that in copper-catalyzed reactions involving triarylbismuth reagents, only one aryl group is usually transferred. In this case, product **16a** was obtained in 75% yield upon running the reaction with 0.7 equivalents of tritolylbismuth (Entry 10). Finally, an erosion in the yield of the reaction was observed upon

conducting the reaction under air (Entry 11) or argon (Entry 12), showing that oxygen is essential to obtain optimal yields. A drastic drop in the yield was also observed when the reaction was performed at room temperature (Entry 13).

Table 1. Optimization of the Reaction Conditions for the Copper-Catalyzed Arylation of BOC-Ala-Tyr-Val-OMe

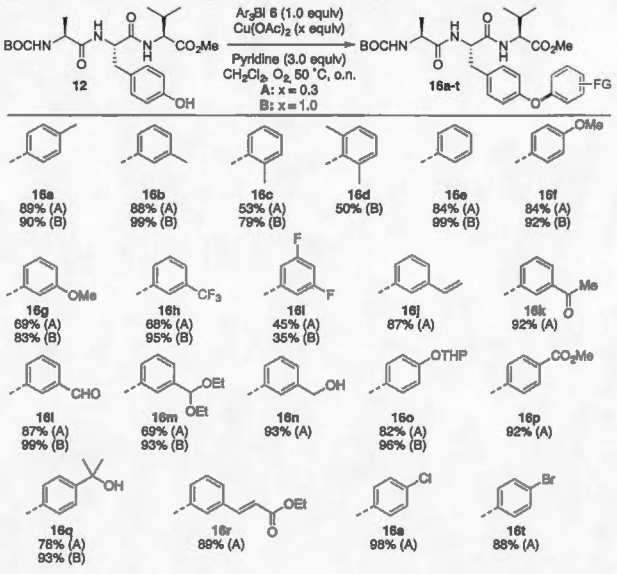


Entry	Change from "*standard conditions*"	Yield (%)[a]
1	No change	90
2	Toluene instead of DCM	79
3	Acetonitrile instead of DCM	27
4	DMF instead of DCM	39
5	THF instead of DCM	77
6	1.0 Equiv of Pyridine instead of 3.0 equiv	84
7	Et_3N instead of Pyridine	83
8	0.3 Equiv $Cu(OAc)_2$ instead of 1.0 equiv	89
9	0.1 Equiv $Cu(OAc)_2$ instead of 1.0 equiv	56
10	0.7 Equiv Tol_3Bi instead of 1.0 equiv	75
11	Air instead of O_2	74
12	Argon instead of O_2	55
13	r.t. instead of 50°C	25

[a] **Yield are for isolated pure product.**

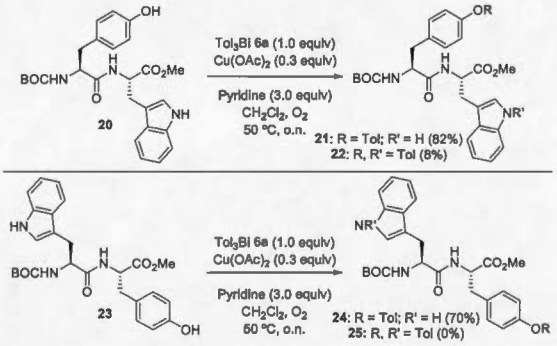
We then performed the arylation reaction on tyrosine-containing tripeptide **12** using diversely substituted triarylbismuthines **6** (**Scheme 5**). The reaction was conducted using 1.0 equivalent of triarylbismuthine, 3.0 equivalents of pyridine, and 0.3 equivalents of copper acetate in dichloromethane at 50 °C under oxygen (Method A). In cases where lower yields were obtained, the reaction was also performed using 1.0 equivalent of copper acetate (Method B). The results show that *para*-, *meta*-, and unsubstituted aryl groups can be transferred with similar efficiency (**16a,b,e**). Interestingly, only a minor reduction in the yield was observed in the transfer of an *ortho*-tolyl group (**16c**), showing that *ortho*-substitution is well tolerated. The method even allowed the installation of a highly hindered 2,6-dimethylphenyl fragment in 50% yield (**16d**). Triarylbismuthines possessing a methoxy group at the para or meta position afforded the corresponding compounds **16f** and **16g**, showing that the presence of electron donating and withdrawing groups is well tolerated. The presence of a trifluoromethyl on the aryl group was also tolerated (**16h**). However, the presence of fluorine atoms at the 3- and 5-positions led to a substantial drop in the yield of the reaction (**16i**). The method showed remarkable functional group tolerance as indicated by the efficient coupling of triarylbismuth reagents possessing a vinyl moiety (**16j**), a methylketone (**16k**), an aldehyde (**16l**), an acetal (**16m**), a primary alcohol (**16n**), a THP-protected phenol (**16o**), a methyl ester (**16p**), a tertiary alcohol (**16q**), an α,β-unsaturated ester (**16r**), a chloride (**16s**) and a bromide (**16t**).

Scheme 5. Copper-Catalyzed Arylation of BOC-Ala-Tyr-Val-OMe Using Various Triarylbismuthines



Method A: Ar_3Bi (1.0 equiv), Pyridine (3.0 equiv), $Cu(OAc)_2$ (0.3 equiv), CH_2Cl_2, O_2, 50°C, o.n.; **Method B:** Ar_3Bi (1.0 equiv), Pyridine (3.0 equiv), $Cu(OAc)_2$ (1.0 equiv), CH_2Cl_2, O_2, 50°C, o.n.

Scheme 6. Chemoselectivity Study in the Arylation of BOC-Tyr-Trp-OMe and BOC-Trp-Tyr-OMe



Next, we evaluated the chemoselectivity of the arylation protocol by performing the reaction on BOC-Tyr-Trp-OMe **20** (**Scheme 6**). Using 0.3 equivalents of copper acetate and tritolylbismuthine, we obtained the corresponding *O*-tolyl peptide **21** in 82% yield along with 8% of the ditolyl product **22**. To test wether the position of the tyrosine had an impact on the outcome of the process, the reaction was also performed on BOC-Trp-Tyr-OMe **23**. In this case, only the *O*-tolyl product **24** was obtained in a slightly reduced yield. Moreover, since none of the ditolyl product **25** was obtained, this suggests that the reactivity of tyrosine is moderately affected by its position in the peptide and/or by their neighbouring amino acids. Surprisingly, we could not isolate any of the product from mono arylation on the indole. The results from arylation on peptide **20** and **23** demonstrate that tyrosine is more reactive than tryptophan in the copper-catalyzed arylation reaction using triarylbismuthines.

In summary, we developed a chemoselective copper-catalyzed O-arylation reaction of small tyrosine-containing peptides. The reaction operates under mild conditions, allows the introduction of *ortho*-, *meta*-, and *para*-substituted aryl groups and shows exceptional functional group tolerance. We demonstrated that the reaction is selective for tyrosine and that the outcome of the process is moderately affected by the position of the tyrosine in the peptide. The application of this method to the arylation of more elaborated peptides is under investigation in our laboratories and results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of NMR and IR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

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Supporting Information

Chemoselective Copper-Catalyzed O-Arylation of Small Tyrosine-Containing Peptides Using Functionnalized Organobismuth Reagents

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EXPERIMENTAL SECTION

General Information: Unless otherwise indicated, all reactions were run under argon in non-flame dried glassware. For reactions performed under oxygen, 99.6% extra dry oxygen was used. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were prepared by conventional methods using metallic magnesium or via Knochel's procedure.[1] Anhydrous bismuth chloride >98% was purchased from Aldrich. Triphenylbismuth diacetate was purchased from Aldrich. Triarylbismuthines **6a**, **6c**, **6g**, **6o** and **6p** were prepared according to a procedure that we previously reported.[2] Triarylbismuthines **6b**, **6l** and **6m** were prepared according to methods previously reported by us.[3] Triarylbismuthines **6d**, **6f**, **6h**, **6i**, **6q** and **6r** were prepared according to a procedure that we previously reported.[4] Organobismuthines **6e**, **6j**, **6k** and **6n** were prepared according to methods we previously reported.[5] Anhydrous solvents were obtained using a MBRAUN (model MB-SPS 800) encapsulated solvent purification system and were further dried over 4 Å molecular sieves. The progress of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230-400 mesh silica (Silicycle) using the indicated solvent system according to standard techniques. Melting points were taken on an Electrothermal Mel-TEMP and are uncorrected. Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on a Bruker Avance-III 300 MHz NanoBay or a Bruker Avance-III HD 600 MHz spectrometer. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.26 ppm; methanol, δ 3.31 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet), coupling constant J in Hz and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.16 ppm) or the central peak of tetradeuteromethanol (δ 49.00 ppm) as the internal standard. IR spectra were recorded on a Thermo Scientific Nicolet 6700 PT-IR from thin films and are reported in reciprocal centimeters (cm-1). HRMS were performed at Université du Québec à Montréal (nanoQAM) on Agilent Technologies, LC 1200 Series / 6210 TOF LCMS analyzer using the electrospray (ESI) mode.

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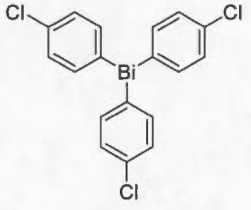
General procedure for the synthesis of triarylbismuthines: Organobismuthines (**6a-i, 6m, 6o** and **6s**) were prepared :according to the following procedure: In a flask equipped with a magnetic stir bar and a condenser, bismuth chloride (500 mg, 1.6 mmol) was dissolved in anhydrous THF (23 mL) under argon and was cooled to –10 °C (ice/acetone bath). The organomagnesium reagent (5.23 mmol) was slowly added dropwise under argon. The reaction mixture was stirred at room temperature for 1 h and heated at 65 °C for 30 minutes. After cooling to room temperature, the solution was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using the indicated solvent system to afford the desired triarylbismuthine.

General procedure for the arylation of amino acids and peptides: Compounds (**11a-i, 16a-t, 17, 18a-b, 19, 21, 22** and **24**) were prepared according to the following procedures: **Method A**: In a sealed tube, the amino acid or peptide (0.1 mmol) was dissolved in non-anhydrous solvent grade dichloromethane (2 mL). The organobismuthine (0.1 mmol) was added followed by copper (II) acetate (0.03 mmol) and pyridine (0.3 mmol). The tube was sealed and heated at 50 °C under O_2 for 16 h. The reaction mixture was cooled to room temperature and silica gel was added. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography using the indicated solvent system to afford the corresponding product. **Method B**: Same as method **A** except that 0.1 mmol of $Cu(OAc)_2$ was used.

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION

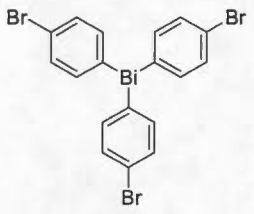
Tris(4-chlorophenyl)bismuthine (6s)



The general procedure was followed on a 3.68 mmol scale starting from bismuth chloride and 4-chlorophenylmagnesium bromide. The crude product was purified on silica gel (2% EtOAc/hexanes) to afford tris(4-chlorophenyl)bismuthine **6s** as a white solid (1.6824 g, 84%): mp 106-107 °C; R_f 0.24 (2% EtOAc/hexanes). ^{1}H-NMR (300 MHz) δ 7.64-7.60 (m, 6H), 7.39-7.35 (m, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ

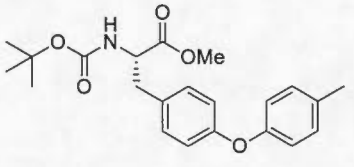
152.9, 138.9, 134.6, 131.1; IR (neat) 3032, 1900, 1556, 1467, 1373, 1176, 1082, 1042, 1001, 805, 711; HRMS (ESI) calcd for $[C_{18}H_{12}Cl_3Bi + HCOO]^-$: 586.9790, found 586.9741.

Tris(4-bromophenyl)bismuthine (6t)



1,4-Dibromobenzene (3.0974g, 13.128 mmol) was added to a flame dried round bottom flask and a magnetic stir bar. 1,4-Dibromobenzene was dissolved in anhydrous THF (13 mL) and the flask was chased with argon and cooled to -78 °C in an acetone/dry ice bath. n-BuLi (2.5 M in hexanes) (11.816 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. In another flame dried round bottom flask, $BiCl_3$ was added, the flask was chased with argon, the $BiCl_3$ was dissolved in anhydrous THF (33 mL) and the solution was cooled to -78 °C in an acetone/dry ice bath. The lithium-halogen exchange solution was transferred to the $BiCl_3$ solution using a double tipped needle and argon pressure. The reaction mixture was stirred at -78°C for 3 h and it was then warmed to room temperature and stirred for 16 h. EtOAc (50 mL) was added to the reaction mixture, it was then diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 X 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4 and concentrated over reduced pressure. The crude product was purified on silica gel (100% hexanes) to afford tris(4-bromophenyl)bismuthine **6t** as a white solid (1.4211 g, 71%): mp 132-133 °C; R_f 0.19 (100% hexanes). ^{1}H-NMR (300 MHz) δ 7.56-7.53 (m, 6H), 7.52-7.49 (m, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 153.5, 139.2, 134.0, 123.1; IR (neat) 3056, 1548, 1467, 1368, 1070, 1037, 993, 792, 686; HRMS (ESI) calcd for $[C_{18}H_{12}Br_3Bi + HCOO]^-$: 718.8275, found 718.8284.

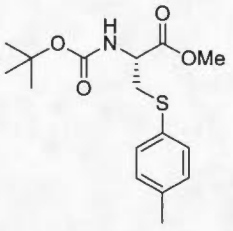
(S)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-(*p*-tolyloxy)phenyl)propanoate (11a)



Method B was followed on a 0.169 mmol scale starting from **10a** and organobismuthine **6a**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **11a** as a colorless oil (64.0 mg, 98%): R_f 0.34 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15-7.12 (m, 2H), 7.08-7.05 (m, 2H), 6.92-6.88 (m, 4H), 5.03-4.75 (m, 1H), 4.60-4.38 (m, 1H), 3.72 (s, 3H), 3.09 (dd, J = 13.8, 5.7 Hz, 1H), 3.00 (dd, J = 14.0,

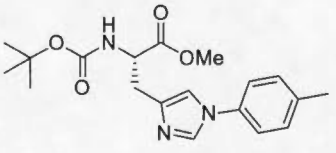
6.1 Hz, 1H), 2.33 (s, 3H), 1.42 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.4, 157.0, 155.2, 154.7, 133.1, 130.6, 130.4, 130.3, 119.3, 118.4, 80.1, 54.6, 52.3, 37.8, 28.4, 20.8; IR (neat) 3371, 3027, 2976, 1744, 1713, 1604, 1498, 1436, 1365, 1235, 1162, 1056, 1015, 873, 814; HRMS (ESI) calcd for $[C_{22}H_{27}NO_5 + Na]^+$: 408.1781, found 408.1795.

(R)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(*p*-tolylthio)propanoate (11b)



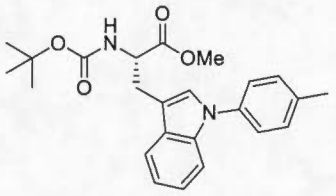
Method B was followed on a 0.215 mmol scale starting from **10b** and organobismuthine **6a**. The crude product was purified on silica gel (0.5% MeOH/CH_2Cl_2) to afford **11b** as a pale yellow oil (61.6 mg, 88%): R_f 0.23 (0.5% MeOH/CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 5.50-4.97 (m, 1H), 4.65-4.20 (m, 1H), 3.53 (s, 3H), 3.31 (d, *J* = 4.9 Hz, 2H), 2.30 (s, 3H), 1.41 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.2, 155.0, 137.4, 131.9, 131.0, 129.9, 80.1, 53.4, 52.4, 37.9, 28.4, 21.1; IR (neat) 3367, 3068, 2974, 2925, 1744, 1712, 1491, 1364, 1160, 1050, 1013, 915, 854, 805, 727; HRMS (ESI) calcd for $[C_{16}H_{23}NO_4S + Na]^+$: 348.1240, found 348.1226.

(S)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(1-(*p*-tolyl)-*1H*-imidazol-4-yl)propanoate (11c)



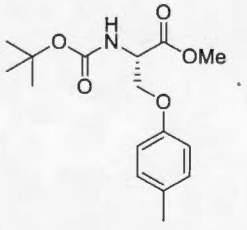
Method B was followed on a 0.186 mmol scale starting from **10c** and organobismuthine **6a**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **11c** as a colorless amorphous paste (54.4 mg, 81%): R_f 0.64 (40% EtOAc/hexanes); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.01 (s, 1H), 5.91-5.42 (m, 1H), 4.60-4.42 (m, 1H), 3.70 (s, 3H), 3.14 (dd, *J* = 14.8, 5.6 Hz, 1H), 3.07 (dd, *J* = 14.8, 4.7 Hz, 1H), 2.37 (s, 3H), 1.42 (s, 9H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 172.6, 155.7, 138.4, 137.5, 135.3, 134.8, 130.4, 121.2, 116.0, 79.7, 53.6, 52.3, 30.3, 28.4, 21.0; IR (neat) 3350, 3129, 2973, 2928, 1741, 1703, 1521, 1483, 1365, 1251, 1159, 1051, 1019, 813; HRMS (ESI) calcd for $[C_{19}H_{25}N_3O_4 + H]^+$: 360.1918, found 360.1922.

(S)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(1-(*p*-tolyl)-*1H*-indol-3-yl)propanoate (11d)



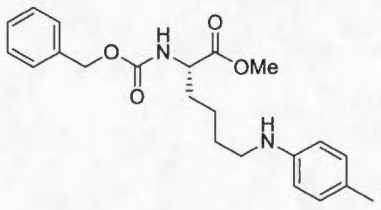
Method B was followed on a 0.157 mmol scale starting from **10d** and organobismuthine **6a**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **11d** as a pale yellow solid (38.2 mg, 60%): mp 87-88 °C; R_f 0.74 (40% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.38-7.30 (m, 4H), 7.25-7.17 (m, 2H), 7.16-7.11 (m, 1H), 5.17-4.89 (m, 1H), 4.75-4.54 (m, 1H), 3.72 (s, 3H), 3.37-3.34 (m, 2H), 2.44 (s, 3H), 1.45 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 155.3, 137.1, 136.4, 136.2, 130.2, 126.7, 124.3, 122.6, 120.2, 119.2, 111.1, 110.7, 79.9, 54.3, 52.4, 28.4, 28.0, 21.1; IR (neat) 3334, 3038, 2920, 2848, 1734, 1684, 1513, 1452, 1291, 1246, 1213, 1159, 1015, 821, 726; HRMS (ESI) calcd for $[C_{24}H_{28}N_2O_4 + Na]^+$: 431.1941, found 431.1945.

(S)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(*p*-tolyloxy)propanoate (11e)



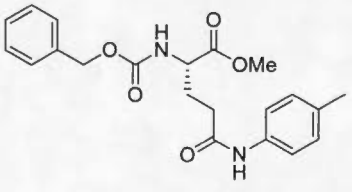
Method B was followed on a 0.228 mmol scale starting from **10e** and organobismuthine **6a**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **11e** as a yellow oil (31.1 mg, 45%): R_f 0.41 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.08-7.06 (m, 2H), 6.78-6.76 (m, 2H), 5.51 (d, *J* = 8.8 Hz, 1H), 4.64 (td, *J* = 8.7, 3.1 Hz, 1H), 4.36 (dd, *J* = 9.3, 2.9 Hz, 1H), 4.16 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.76 (s, 3H), 2.28 (s, 3H), 1.46 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.7, 156.3, 155.5, 130.9, 130.0, 114.7, 80.3, 68.6, 53.8, 52.7, 28.4, 20.6; IR (neat) 3379, 2974, 2925, 1748, 1708, 1503, 1360, 1230, 1156, 1058, 817; HRMS (ESI) calcd for $[C_{16}H_{23}NO_5 + Na]^+$: 332.1468, found 332.1483.

(S)-Methyl 2-(((benzyloxy)carbonyl)amino)-6-(*p*-tolylamino)hexanoate (11f)



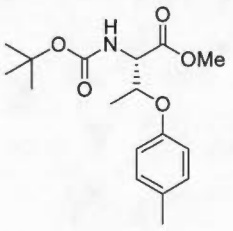
Method B was followed on a 0.306 mmol scale starting from **10f** and organobismuthine **6a**. The crude product was purified on silica gel (30% EtOAc/hexanes) to afford **11f** as an orange oil (40.2 mg, 35%): R_f 0.48 (40% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38-7.34 (m, 5H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.52 (d, *J* = 8.1 Hz, 2H), 5.34 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 2H), 4.41 (q, *J* = 7.7 Hz, 1H), 3.74 (s, 3H), 3.08 (t, *J* = 6.8 Hz, 2H), 2.24 (s, 3H), 1.94-1.85 (m, 1H), 1.73-1.68 (m, 1H), 1.66-1.58 (m, 2H), 1.48-1.40 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.0, 156.0, 146.1, 136.3, 129.8, 128.6, 128.3, 128.2, 126.6, 113.0, 67.2, 53.8, 52.5, 44.1, 32.7, 29.2, 22.9, 20.5; IR (neat) 3369, 3030, 2947, 2863, 1711, 1616, 1517, 1448, 1254, 1209, 1042, 908, 806, 749, 692; HRMS (ESI) calcd for $[C_{22}H_{28}N_2O_4 + H]^+$: 385.2122, found 385.2129.

(S)-Methyl 2-(((benzyloxy)carbonyl)amino)-5-oxo-5-(*p*-tolylamino)pentanoate (11g)



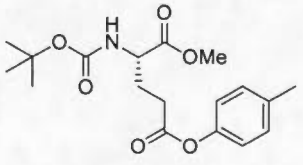
Method B was followed on a 0.169 mmol scale starting from **10g** and organobismuthine **6a**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **11g** as a white solid (22.4 mg, 34%): mp 131-132 °C; R_f 0.28 (40% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (s(br), 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.36-7.33 (m, 5H), 7.08 (d, *J* = 8.2 Hz, 2H), 5.82 (d, *J* = 8.0 Hz, 1H), 5.08 (s, 2H), 4.40 (dt, *J* = 9.2, 3.9 Hz, 1H) 3.70 (s, 3H), 2.42-2.40 (m, 2H), 2.30 (s, 3H), 2.28-2.18 (m, 1H), 2.04-1.97 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.4, 170.2, 156.8, 136.1, 135.6, 134.0, 129.6, 128.7, 128.4, 128.3, 120.0, 67.4, 53.5, 52.8, 33.8, 29.5, 21.0; IR (neat) 3334, 3293, 3125, 3034, 2950, 2920, 2848, 1726, 1684, 1658, 1597, 1528, 1433, 1270, 1220, 1159, 1019, 969, 817, 688 ; HRMS (ESI) calcd for $[C_{21}H_{24}N_2O_5 + H]^+$: 385.1758, found 385.1776.

(2S,3S)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(*p*-tolyloxy)butanoate (11h)



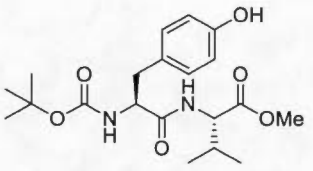
Method B was followed on a 0.214 mmol scale starting from **10h** and organobismuthine **6a**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **11h** as a colorless oil (14.4 mg, 21%): R_f 0.32 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.07-7.04 (m, 2H), 6.79-6.76 (m, 2H), 5.40 (d, *J* = 9.7 Hz, 1H), 4.89 (dq, *J* = 12.5, 2.31 Hz, 1H), 4.47 (dd, *J* = 9.7, 2.4 Hz, 1H), 3.67 (s, 3H), 2.27 (s, 3H), 1.49 (s, 9H), 1.32 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.2, 156.3, 155.1, 131.2, 130.1, 116.6, 80.2, 74.8, 58.1, 52.6, 28.5, 20.6, 16.5; IR (neat) 3441, 3030, 2977, 2867, 1753, 1715, 1502, 1220, 1159, 1068, 905, 806; HRMS (ESI) calcd for $[C_{17}H_{25}NO_5 + Na]^+$: 346.1625, found 346.1635.

(S)-1-Methyl 5-*p*-tolyl 2-((*tert*-butoxycarbonyl)amino)pentanedioate (11i)



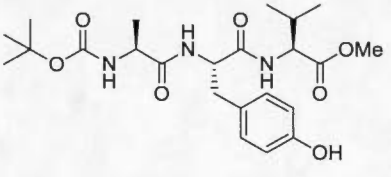
Method B was followed on a 0.191 mmol scale starting from **10i** and organobismuthine **6a**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **11i** as a yellow oil (10.7 mg, 16%): R_f 0.26 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 5.15 (d, *J* = 7.9 Hz, 1H), 4.42 (q, *J* = 5.3 Hz, 1H), 3.76 (s, 3H), 2.74-2.56 (m, 2H), 2.34 (s, 3H), 2.32-2.26 (m, 1H), 2.13-2.00 (m, 1H), 1.45 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.7, 171.6, 155.5, 148.5, 135.6, 130.0, 121.3, 80.3, 53.0, 52.6, 30.6, 28.4, 27.9, 21.0; IR (neat) 3375, 3032, 2974, 2921, 2848, 1748, 1711.7, 1503, 1446, 1360, 1189, 1164, 1140, 1050, 1013, 805; HRMS (ESI) calcd for $[C_{18}H_{25}NO_6 + Na]^+$: 374.1574, found 374.1579.

(S)-Methyl 2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)-3-methylbutanoate (12i)



Boc-Tyr-OH (3.564 g, 12.67 mmol), H-Val-OMe•HCl (2.124 g, 12.67 mmol) and HCTU (5.767 g, 13.94 mmol) were dissolved in CH_2Cl_2 (127 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (7.72 mL, 44.34 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **12i** as a white solid (4.07 g, 81%): mp 72-73 °C; R_f 0.59 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 7.9 Hz, 2H), 6.94-6.78 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.47 (s(br), 1H), 5.29-4.85 (m, 1H), 4.59-4.37 (m, 1H), 4.37-4.08 (m, 1H), 3.68 (s, 3H), 2.96 (d, *J* = 6.9 Hz, 2H), 2.12-2.05 (m, 1H), 1.42 (s, 9H), 0.87 (d, *J* = 7.4 Hz, 3H), 0.84 (d, *J* = 7.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.9, 171.7, 155.7, 155.4, 130.5, 127.9, 115.7, 80.7, 57.5, 56.2, 52.3, 37.4, 31.4, 28.4, 18.9, 17.9; IR (neat) 3306, 3065, 2968, 1734, 1655, 1615, 1515, 1438, 1366, 1224, 1162, 1047, 1018, 828; HRMS (ESI) calcd for $[C_{20}H_{30}N_2O_6 + H]^+$: 395.2177, found 395.2166.

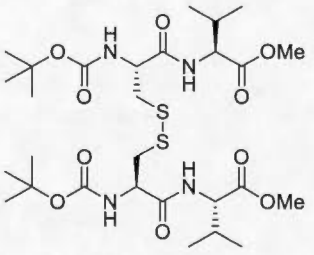
(6S,9S,12S)-Methyl 9-(4-hydroxybenzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (12)



12i (2.462 g, 6.24 mmol) was dissolved in CH_2Cl_2 (37.20 mL) in a round bottom flask with a stir bar. The flask was chased with argon and cooled to 0 °C in an ice bath. TFA (24.80 mL, 323.87 mmol) was added dropwise, the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (100 mL), diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq.

$NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The *N*-deprotected product (1.582 g, 5.37 mmol), Boc-Ala-OH (1.016 g, 5.37 mmol) and HCTU (2.443 g, 5.91 mmol) were dissolved in CH_2Cl_2 (54 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (3.27 mL, 18.79 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (60% EtOAc/hexanes) to afford **12** as a white solid (1.908 g, 76% over 2 steps): mp 95-96 °C; R_f 0.32 (4% MeOH/CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 7.5 Hz, 1H), 6.29 (s(br), 1H), 5.03 (d, *J* = 7.1 Hz, 1H), 4.62 (q, *J* = 6.5 Hz, 1H), 4.42 (dd, *J* = 8.6, 5.3 Hz, 1H), 4.14 (quint, *J* = 6.3 Hz, 1H), 3.70 (s, 3H), 2.99-2.97 (m, 2H), 2.14-2.03 (m, 1H), 1.42 (s, 9H), 1.29 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.2, 171.9, 171.3, 155.7, 155.6, 130.5, 127.3, 115.7, 80.4, 57.6, 54.7, 52.3, 50.3, 37.4, 31.3, 28.4, 18.9, 18.5, 18.0; IR (neat) 3289, 3080, 2971, 1646, 1615, 1515, 1447, 1366, 1226, 1162, 1021, 852, 754; HRMS (ESI) calcd for $[C_{23}H_{35}N_3O_7 + H]^+$: 466.2548, found 466.2563.

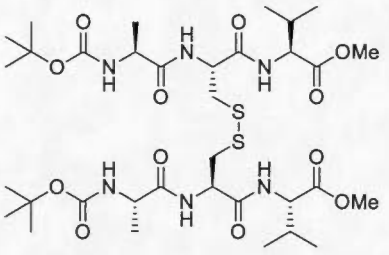
(2S,2'S)-Dimethyl 2,2'-(((2R,2'R)-3,3'-disulfanediylbis(2-((*tert*-butoxycarbonyl)amino)propanoyl))bis(azanediyl))bis(3-methylbutanoate) (13i)



$(Boc\text{-}Cys\text{-}OH)_2$ (3.282 g, 7.45 mmol), H-Val-OMe•HCl (2.500 g, 14.90 mmol) and HCTU (6.780 g, 16.39 mmol) were dissolved in CH_2Cl_2 (75 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (9.08 mL, 52.15 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **13i** as a white solid (4.304 g, 86%): mp 136-137 °C; R_f 0.36 (40% EtOAc/hexanes);

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 2H), 5.56 (d, *J* = 8.9 Hz, 2H), 4.70-4.67 (m, 2H), 4.48 (dd, *J* = 9.0, 6.3 Hz, 2H), 3.71 (s, 6H), 3.12-2.97 (m, 4H), 2.26-2.12 (m, 2H), 1.45 (s, 18H), 0.95 (d, *J* = 7.1 Hz, 6H), 0.94 (d, *J* = 6.8 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.1, 170.5, 155.7, 80.4, 57.9, 54.1, 52.2, 44.9, 31.0, 28.4, 19.3, 18.5; IR (neat) 3322, 3072, 2966, 1740, 1667, 1516, 1315, 1274, 1246, 1209, 1164, 1017, 862, 760, 645; HRMS (ESI) calcd for $[C_{28}H_{50}N_4O_{10}S_2 + H]^+$: 667.3041, found 667.3072.

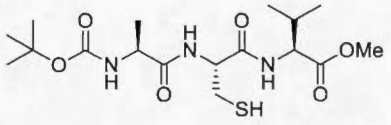
(6S,6'S,9R,9'R,12S,12'S)-Dimethyl 9,9'-(disulfanediylbis(methylene))bis(12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate) (13ii)



13i (4.275 g, 6.37 mmol) was dissolved in CH_2Cl_2 (38.40 mL) in a round bottom flask with a stir bar. The flask was chased with argon and cooled to 0 °C in an ice bath. TFA (25.6 mL, 334.31 mmol) was added dropwise, the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (100 mL), diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The *N*-deprotected product (2.735 g, 5.86 mmol), Boc-Ala-OH (1.109 g, 5.86 mmol) and HCTU (2.667 g, 6.45 mmol) were dissolved in CH_2Cl_2 (59 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (3.57 mL, 20.51 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (60% EtOAc/hexanes) to afford **13ii** as a white solid (4.009 g, 78% over 2 steps): mp 107-108 °C; R_f 0.61 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.1 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 5.54-5.48 (m, 2H), 5.38 (d, *J* = 6.2 Hz, 2H), 4.47 (dd, *J* = 7.7, 5.2 Hz, 2H), 4.35-4.18 (m, 2H), 3.73 (s, 6H), 3.06 (dd, *J* = 14.8, 3.0 Hz, 2H), 2.84 (dd, *J* = 14.5, 11.0 Hz, 2H), 2.26-2.15 (m, 2H), 1.43 (s, 18H), 1.36 (d, *J* = 7.0 Hz, 6H), 0.98 (d, *J* = 6.8 Hz, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.6, 172.3, 170.3, 155.5, 80.2, 57.8, 52.8, 52.2, 50.7, 46.3, 31.1, 28.5, 19.2, 18.8, 18.1; IR (neat) 3289, 3077, 2970, 2933, 1740, 1712, 1646, 1507,

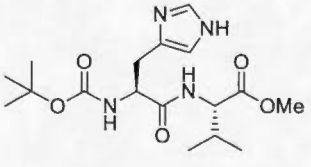
1360, 1246, 1156, 1054, 1025, 858, 731; HRMS (ESI) calcd for $[C_{34}H_{60}N_6O_{12}S_2 + H]^+$: 809.3783, found 809.3750.

(6S,9R,12S)-Methyl 12-isopropyl-9-(mercaptomethyl)-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (13)



13ii (3.712 g, 4.59 mmol) was dissolved in n-propanol (72.80 mL) and water (36.40 mL) in a round bottom flask with a stir bar. The pH was adjusted to 8 using NH_4OH (30 M) and the flask was chased with argon. Tri-n-butylphosphine (1.74 mL, 6.88 mmol) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The pH was adjusted to 6 using HCl (12 M), the reaction mixture was diluted with sat. aq. NaCl (100 mL) and extracted with $CHCl_3$ (3 X 100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **13** as a white solid (2.82 g, 76%): mp 90-91 °C; R_f 0.39 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 5.10 (d, *J* = 6.3 Hz, 1H), 4.68 (q, *J* = 6.3 Hz, 1H), 4.48 (dd, *J* = 8.4, 5.1 Hz, 1H), 4.20 (quint, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 3.11-3.02 (m, 1H), 2.79-2.69 (m, 1H), 2.24-2.13 (m, 1H), 1.76 (t, *J* = 8.6 Hz, 1H), 1.43 (s, 9H), 1.37 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.0, 172.0, 169.7, 155.7, 80.6, 57.7, 54.4, 52.3, 50.5, 31.0, 28.4, 26.6, 19.2, 18.2, 17.9; IR (neat) 3297, 3072, 2966, 2929, 2876, 2553, 1744, 1642, 1511, 1454, 1360, 1454, 1360, 1246, 1205, 1160, 1017, 854, 751; HRMS (ESI) calcd for $[C_{17}H_{31}N_3O_6S + H]^+$: 406.2006, found 406.2020.

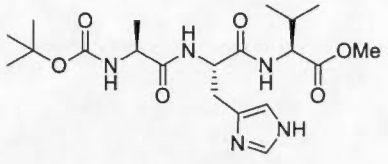
(S)-Methyl 2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(*1H*-imidazol-4-yl)propanamido)-3-methylbutanoate (14i)



Boc-His-OH (2.905 g, 11.38 mmol), H-Val-OMe•HCl (1.908 g, 11.38 mmol) and HCTU (5.179 g, 12.52 mmol) were dissolved in CH_2Cl_2 (110 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (6.94 mL, 39.83 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was

diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (2.5% MeOH/CH_2Cl_2) to afford **14i** as a colorless oil (2.3663 g, 56%): R_f 0.44 (10% MeOH/CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60-7.30 (m, 1H), 7.52 (s, 1H), 6.80 (s, 1H), 6.25-5.80 (m, 1H), 4.42-4.38 (m, 2H), 3.69 (s, 3H), 3.11 (dd, *J* = 14.9, 4.2 Hz, 1H), 2.98 (dd, *J* = 14.8, 6.2 Hz, 1H), 2.14-2.04 (m, 1H), 1.42 (s, 9H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.3, 172.2, 156.0, 135.1, 132.2, 119.1, 80.4, 57.7, 54.2, 52.3, 31.0, 29.0, 28.4, 19.0, 17.8; IR (neat) 3292, 3085, 2962, 2920, 2848, 1741, 1661, 1517, 1361, 1251, 1163, 1019, 931, 855, 821, 753, 658; HRMS (ESI) calcd for $[C_{17}H_{28}N_4O_5 + H]^+$: 369.2132, found 369.2130.

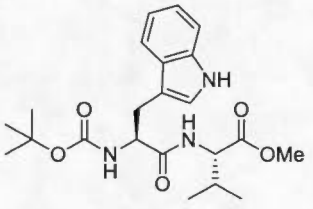
(6S,9S,12S)-Methyl 9-((*1H*-imidazol-4-yl)methyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (14)



14i (252 mg, 0.68 mmol) was dissolved in CH_2Cl_2 (4.00 mL) in a round bottom flask with a stir bar. The flask was chased with argon and cooled to 0 °C in an ice bath. TFA (2.72 mL, 32.91 mmol) was added dropwise, the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (50 mL), diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 X 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 50 mL), sat. aq. NaCl (2 X 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The *N*-deprotected product (164 mg, 0.61 mmol), Boc-Ala-OH (115 mg, 0.61 mmol) and HCTU (278 mg, 0.67 mmol) were dissolved in CH_2Cl_2 (6.1 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (796 µL, 2.14 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 X 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 50 mL), sat. aq. NaCl (2 X 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (7.5% MeOH/CH_2Cl_2) to afford **14** as a white solid (174 mg, 58% over 2 steps): mp 81-82 °C; R_f 0.32 (10% MeOH/CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (s(br), 1H), 7.78-7.58 (m, 1H), 7.51 (s, 1H), 7.15-6.05

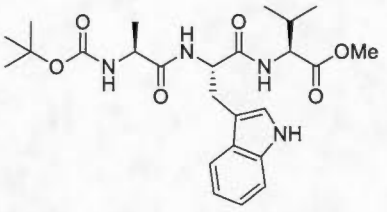
(s(br), 1H), 6.78 (s, 1H), 5.60-5.25 (m, 1H), 4.73 (q, J = 5.7 Hz, 1H), 4.38 (dd, J = 8.2, 5.2 Hz, 1H), 4.18 (quint, J = 6.8 Hz, 1H) 3.70 (s, 3H), 3.11 (dd, J = 15.1, 5.1 Hz, 1H), 3.02 (dd, J = 14.9, 5.9 Hz, 1H), 2.16-2.05 (m, 1H), 1.41 (s, 9H), 1.36 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 173.5, 172.3, 171.3, 155.8, 134.9, 131.9, 119.0, 80.1, 57.9, 53.2, 52.2, 50.6, 30.8, 28.8, 28.4, 19.0, 18.5, 17.9; IR (neat) 3285, 3077, 2973, 2931, 1737, 1650, 1517, 1441, 1365, 1251, 1159, 1015, 840, 753; HRMS (ESI) calcd for $[C_{20}H_{33}N_5O_6 + H]^+$: 440.2504, found 440.2494.

(S)-Methyl 2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(*1H*-indol-3-yl)propanamido)-3-methylbutanoate (15i)



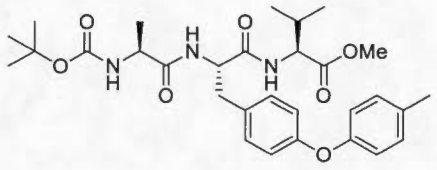
Boc-Trp-OH (750 mg, 2.46 mmol), H-Val-OMe•HCl (413 mg, 2.46 mmol) and HCTU (1.121 g, 2.71 mmol) were dissolved in CH_2Cl_2 (25 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (1.50 mL, 8.62 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 X 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 50 mL), sat. aq. NaCl (2 X 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **15i** as a white solid (983.7 mg, 96%): mp 68-69 °C; R_f 0.24 (40% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (s(br), 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.19 (dt, J = 7.1, 1.0 Hz, 1H), 7.11 (dt, J = 7.1, 0.9 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 6.35 (d, J = 8.3 Hz, 1H), 5.09 (s(br), 1H), 4.62-4.47 (m, 1H), 4.44 (dd, J = 8.6, 4.8 Hz, 1H), 3.64 (s, 3H), 3.32 (dd, J = 14.7, 5.9 Hz, 1H), 3.20 (dd, J = 14.6, 7.0 Hz, 1H), 2.04-1.93 (m, 1H), 1.41 (s, 9H), 0.76 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.1, 172.0, 155.6, 136.4, 127.5, 123.3, 122.2, 119.7, 118.8, 111.4, 110.2, 80.3, 57.2, 55.3, 52.1, 31.1, 28.3, 28.2, 18.7, 17.6; IR (neat) 3326, 3056, 2966, 2938, 1659, 1507, 1364, 1246, 1152, 1005, 854, 739, 539; HRMS (ESI) calcd for $[C_{22}H_{31}N_3O_5 + Na]^+$: 440.2156, found 440.2175.

(6S,9S,12S)-Methyl 9-((*1H*-indol-3-yl)methyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (15)



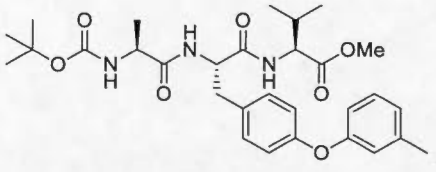
15i (765 mg, 1.84 mmol) was dissolved in CH_2Cl_2 (10.80 mL) in a round bottom flask with a stir bar. The flask was chased with argon and cooled to 0 °C in an ice bath. TFA (7.20 mL, 94.03 mmol) was added dropwise, the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (100 mL), diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The *N*-deprotected product (528 mg, 1.67 mmol), Boc-Ala-OH (316 mg, 1.67 mmol) and HCTU (759 mg, 1.83 mmol) were dissolved in CH_2Cl_2 (17.00 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (1.02 mL, 5.83 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 X 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 50 mL), sat. aq. NaCl (2 X 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (60% EtOAc/hexanes) to afford **15** as a white solid (550.4 mg, 61% over 2 steps): mp 175-176 °C; R_f 0.24 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (s(br), 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.19 (dt, *J* = 7.1, 1.2 Hz, 1H) 7.13 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.11-7.10 (m, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.32 (d, *J* = 8.3 Hz, 1H), 4.92 (d, *J* = 7.0 Hz, 1H), 4.77-4.70 (m, 1H), 4.36 (dd, *J* = 8.4, 5.1 Hz, 1H), 4.12 (quint, *J* = 7.1 Hz, 1H), 3.64 (s, 3H), 3.34 (dd, *J* = 14.6, 5.3 Hz, 1H), 3.16 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.07-1.96 (m, 1H), 1.38 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.9, 171.9, 171.3, 155.5, 136.3, 127.6, 123.7, 122.2, 119.7, 118.8, 111.4, 110.3, 80.3, 57.7, 54.1, 52.2, 50.6, 31.1, 28.3, 28.0, 18.9, 18.5, 17.9; IR (neat) 3391, 3346, 3258, 3064, 2969, 2943, 1745, 1696, 1669, 1639, 1521, 1486, 1361, 1251, 1159, 1091, 1019, 848, 741, 673; HRMS (ESI) calcd for $[C_{25}H_{36}N_4O_6 + H]^+$: 489.2708, found 489.2727.

(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-(4-(*p*-tolyloxy)benzyl)-3-oxa-5,8,11-triazatridecan-13-oate (16a)



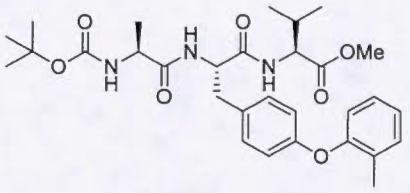
Method B was followed on a 0.107 mmol scale starting from **12** and organobismuthine **6a**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16a** as a white solid (53.3 mg, 90%): mp 77-78 °C; R_f 0.51 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14-7.09 (m, 4H), 6.89-6.85 (m, 5H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 4.69 (q, *J* = 7.1 Hz, 1H), 4.42 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.17 (quint, *J* = 7.4 Hz, 1H), 3.70 (s, 3H) 3.11-2.91 (m, 2H), 2.31 (s, 3H), 2.14-2.03 (m, 1H), 1.41 (s, 9H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.7, 156.9, 155.5, 154.7, 133.0, 130.7, 130.6, 130.3, 119.1, 118.4, 80.3, 57.4, 54.6, 52.2, 50.4, 37.5, 31.3, 28.4, 20.8, 19.0, 18.5, 17.9; IR (neat) 3282, 3068, 2968, 2929, 1742, 1644, 1499, 1445, 1391, 1366, 1162, 1011, 870, 813, 753; HRMS (ESI) calcd for $[C_{30}H_{41}N_3O_7 + H^+]^+$: 556.3017, found 556.3013.

(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-(4-(*m*-tolyloxy)benzyl)-3-oxa-5,8,11-triazatridecan-13-oate (16b)



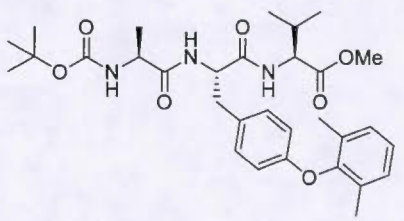
Method B was followed on a 0.0644 mmol scale starting from **12** and organobismuthine **6b**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16b** as a white solid (35.8 mg, 99%): mp 72-73 °C; R_f 0.51 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 7.7 Hz, 1H), 7.17-7.15 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 3H), 6.81-6.75 (m, 3H), 6.40 (d, *J* = 8.5 Hz, 1H), 4.95 (d, *J* = 7.1 Hz, 1H), 4.65 (q, *J* = 7.2 Hz, 1H), 4.43 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.15 (quint, *J* = 7.1 Hz, 1H), 3.70 (s, 3H), 3.07-3.03 (m, 2H), 2.32 (s, 3H), 2.13-2.04 (m, 1H), 1.42 (s, 9H), 1.32 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 7.5 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.7, 171.8, 170.6, 157.2, 156.5, 155.5, 140.0, 131.0, 130.7, 129.6, 124.2, 119.7, 119.0, 116.0, 80.5, 57.5, 54.6, 52.3, 50.5, 37.5, 31.3, 28.4, 21.5, 19.0, 18.4, 17.9; IR (neat) 3281, 3072, 2965, 2924, 2852, 1741, 1642, 1505, 1365, 1258, 1216, 1163, 1015, 931, 855, 779, 684; HRMS (ESI) calcd for $[C_{30}H_{41}N_3O_7 + H]^+$: 556.3017, found 556.3012.

(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-(4-(*o*-tolyloxy)benzyl)-3-oxa-5,8,11-triazatridecan-13-oate (16c)



Method A was followed on a 0.107 mmol scale starting from **12** and organobismuthine **6c**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16c** as a brown-yellow solid (31.7 mg, 53%): mp 81-82 °C; R_f 0.43 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.3 Hz, 1H), 7.16-7.10 (m, 3H), 7.07-7.01 (m, 1H), 6.88-6.79 (m, 4H), 6.55-6.51 (m, 1H), 5.04 (d, *J* = 7.1 Hz, 1H), 4.67 (q, *J* = 7.1 Hz, 1H), 4.43 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.16 (quint, *J* = 7.4 Hz, 1H), 3.69 (s, 3H), 3.04-3.01 (m, 2H), 2.21 (s, 3H), 2.14-2.03 (m, 1H), 1.41 (s, 9H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.7, 157.0, 155.5, 154.6, 131.5, 130.7, 130.3, 129.9, 127.2, 124.0, 119.6, 117.6, 80.3, 57.5, 54.6, 53.5, 52.2, 50.4, 37.4, 31.2, 28.4, 19.0, 18.5, 17.9, 16.2; IR (neat) 3280, 3072, 2966, 2933, 1642, 1511, 1356, 1238, 1160, 1021, 878, 747; HRMS (ESI) calcd for $[C_{30}H_{41}N_3O_7 + H]^+$: 556.3017, found 556.3014.

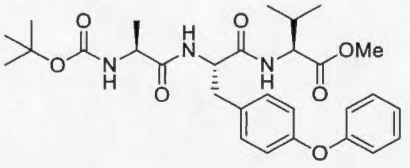
(6S,9S,12S)-Methyl 9-(4-(2,6-dimethylphenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16d)



Method B was followed on a 0.0642 mmol scale starting from **12** and organobismuthine **6d**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16d** as a yellow oil (18.2 mg, 50%): R_f 0.49 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11-7.08 (m, 2H), 7.07-7.04 (m, 2H), 6.95-6.93 (m, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.69-6.65 (m, 2H), 6.37 (d, *J* = 6.2 Hz, 1H), 4.89 (d, *J* = 5.1 Hz, 1H), 4.61 (q, *J* = 7.0 Hz, 1H), 4.41 (dd, *J* = 8.5, 5.0 Hz, 1H), 4.13 (quint, *J* = 6.1 Hz, 1H), 3.70 (s, 3H), 3.01 (d, *J* = 6.8 Hz, 2H), 2.10 (s, 6H), 2.04-1.98 (m, 1H), 1.41 (s, 9H), 1.29 (d, *J* = 7.1 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H) ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.7, 171.8, 170.7, 157.1, 155.6, 151.2, 131.5, 130.7, 129.2, 129.1, 125.2, 114.9, 80.5, 57.5, 54.6, 52.2, 50.5, 37.2, 31.2, 28.4, 19.0, 18.4, 17.9, 16.5; IR (neat) 3283,

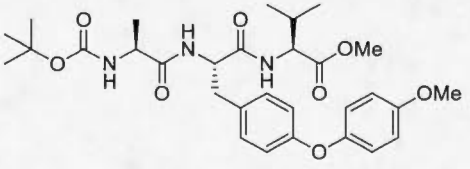
3074, 2969, 2930, 2876, 2855, 1747, 1699, 1650, 1547, 1506, 1472, 1393, 1368, 1223, 1186, 1170, 1026, 872, 771; HRMS (ESI) calcd for $[C_{31}H_{43}N_3O_7 + H]^+$: 570.3174, found 570.3153.

(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-(4-phenoxybenzyl)-3-oxa-5,8,11-triazatridecan-13-oate (16e)



Method B was followed on a 0.107 mmol scale starting from **12** and organobismuthine **6e**. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **16e** as a light brown solid (48.6 mg, 83%): mp 88-89 °C; R_f 0.46 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.16-7.13 (m, 2H), 7.10-7.04 (m, 1H), 6.99-6.94 (m, 3H), 6.92-6.87 (m, 2H), 6.68 (d, *J* = 5.5 Hz, 1H), 5.17 (d, *J* = 7.3 Hz, 1H), 4.74 (q, *J* = 7.2 Hz, 1H), 4.44 (dd, *J* = 8.4, 5.2 Hz, 1H), 4.19 (quint, *J* = 7.2 Hz, 1H), 3.69 (s, 3H), 3.02 (d, *J* = 6.9 Hz, 2H), 2.12-2.03 (m, 1H), 1.40 (s, 9H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.9, 171.8, 170.8, 157.2, 156.3, 155.5, 131.2, 130.8, 129.8, 123.3, 119.0, 118.9, 80.2, 57.4, 54.5, 52.2, 50.3, 37.6, 31.3, 28.4, 19.0, 18.6, 17.9; IR (neat) 3281, 3072, 2966, 2925, 1638, 1486, 1230, 1160, 1017, 866, 751; HRMS (ESI) calcd for $[C_{29}H_{39}N_3O_7 + H]^+$: 542.2861, found 542.2866.

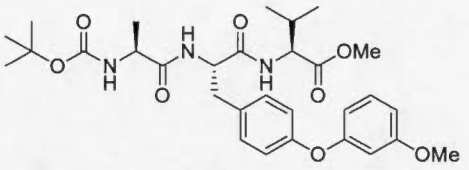
(6S,9S,12S)-Methyl 12-isopropyl-9-(4-(4-methoxyphenoxy)benzyl)-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16f)



Method B was followed on a 0.0651 mmol scale starting from **12** and organobismuthine **6f**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16f** as a white solid (34.5 mg, 92%): mp 63-64 °C; R_f 0.51 (60% EtOAc/hexanes); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.95-6.94 (m, 2H), 6.87-6.84 (m, 2H), 6.84-6.83 (m, 2H), 6.82-6.80 (m, 1H), 6.53-6.38 (m, 1H), 5.05-4.90 (m, 1H), 4.65 (q, *J* = 7.4 Hz, 1H), 4.42 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.20-4.10 (m, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.04 (dd, *J* = 13.9, 6.1 Hz, 1H), 3.00 (dd, *J* = 13.8, 7.3 Hz, 1H), 2.11-2.06 (m, 1H), 1.41 (s, 9H), 1.31 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.7, 157.7, 156.0, 155.5,

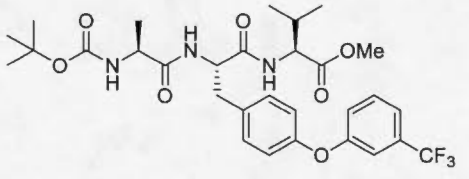
150.2, 130.6, 130.4, 120.9, 117.8, 115.0, 80.4, 57.5, 55.8, 54.7, 52.3, 50.4, 37.3, 31.3, 28.4, 19.0, 18.4, 17.9; IR (neat) 3277, 3068, 2962, 2925, 2872, 2852, 1740, 1691, 1646, 1495, 1368, 1225, 1164, 1029, 825; HRMS (ESI) calcd for $[C_{30}H_{41}N_3O_8 + H]^+$: 572.2966, found 572.2998.

(6S,9S,12S)-Methyl 12-isopropyl-9-(4-(3-methoxyphenoxy)benzyl)-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16g)



Method B was followed on a 0.108 mmol scale starting from **12** and organobismuthine **6g**. The crude product was purified on silica gel (3% MeOH/CH_2Cl_2) to afford **16g** as an orange-brown solid (51.4 mg, 83%): mp 69-70 °C; R_f 0.32 (5% MeOH/CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22-7.14 (m, 3H), 6.93-6.90 (m, 2H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.63 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1H), 6.56-6.53 (m, 2H), 6.53-6.47 (m, 1H), 5.05 (d, *J* = 7.1 Hz, 1H), 4.68 (q, *J* = 7.2 Hz, 1H), 4.43 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.16 (quint, *J* = 7.6 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.04 (d, *J* = 6.9 Hz, 2H), 2.14-2.03 (m, 1H), 1.41 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.6, 161.1, 158.5, 156.1, 155.5, 131.4, 130.8, 130.2, 119.2, 111.0, 108.9, 105.0, 80.4, 57.5, 55.5, 54.6, 52.3, 50.4, 37.5, 31.3, 28.4, 19.0, 18.5, 17.9; IR (neat) 3285, 3072, 2966, 2921, 2848, 1642, 1483, 1213, 1164, 1131, 1042, 952, 854, 768, 682; HRMS (ESI) calcd for $[C_{30}H_{41}N_3O_8 + H]^+$: 572.2966, found 572.2973.

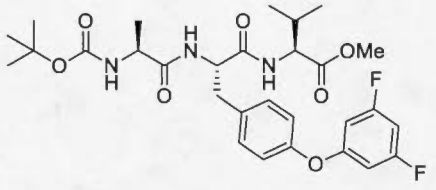
(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-(4-(3-(trifluoromethyl)phenoxy)benzyl)-3-oxa-5,8,11-triazatridecan-13-oate (16h)



Method B was followed on a 0.107 mmol scale starting from **12** and organobismuthine **6h**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16h** as a pale yellow solid (44.4 mg, 68%): mp 78-79 °C; R_f 0.44 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.20-7.18 (m, 3H), 7.13-7.10 (m, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.94-6.89 (m, 2H), 6.76-6.68 (m, 1H), 5.16 (d, *J* = 7.4 Hz, 1H), 4.75 (q, *J* = 7.1 Hz, 1H), 4.45 (dd, *J* = 8.7, 5.2 Hz, 1H), 4.20 (quint, *J* = 6.3 Hz, 1H), 3.68 (s, 3H), 3.04 (d, *J* = 6.9 Hz, 2H), 2.14-2.01 (m, 1H), 1.40 (s, 9H), 1.30 (d, J = 7.0 Hz, 3H), 0.85 (d, *J*

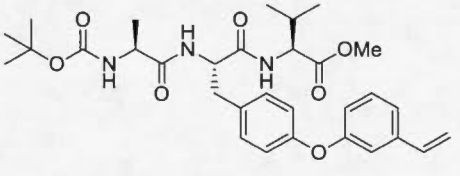
= 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.0, 171.9, 170.8, 157.9, 155.5, 155.2, 132.5, 132.4, 132.1, 131.1, 130.4, 125.6, 122.0, 121.6, 119.8, 119.73, 119.67, 119.6, 119.5, 115.44, 115.40, 115.34, 115.30, 113.4, 80.2, 57.4, 54.5, 52.2, 50.4, 37.7, 31.3, 28.4, 19.0, 18.5, 17.9; IR (neat) 3285, 3072, 2970, 2933, 1646, 1503, 1442, 1324, 1230, 1156, 1123, 1062, 915, 694; HRMS (ESI) calcd for $[C_{30}H_{38}F_3N_3O_7 + H]^+$: 610.2735, found 610.2732.

(6S,9S,12S)-Methyl 9-(4-(3,5-difluorophenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16i)



Method A was followed on a 0.085 mmol scale starting from **12** and organobismuthine **6i**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16i** as a white solid (22.2 mg, 45%): mp 141-142 °C; R_f 0.34 (40% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.97-6.94 (m, 2H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.53-6.52 (m, 1H), 6.51-6.44 (m, 3H), 5.03 (d, *J* = 7.2 Hz, 1H), 4.70 (q, *J* = 7.2 Hz, 1H), 4.44 (dd, *J* = 8.6, 5.0 Hz, 1H), 4.16 (quint, *J* = 6.9 Hz, 1H), 3.69 (s, 3H), 3.06 (d, *J* = 6.9 Hz, 2H), 2.15-2.04 (m, 1H), 1.41 (s, 9H), 1.31 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.5, 165.5, 165.3, 162.2, 162.0, 160.1, 159.8, 159.8, 155.5, 154.5, 133.0, 131.1, 120.3, 101.7, 101.3, 98.7, 98.4, 98.1, 80.4, 57.4, 54.6, 52.3, 50.5, 37.6, 31.3, 28.4, 19.0, 18.4, 17.9; IR (neat) 3323, 3283, 3091, 2966, 2931, 2971, 1741, 1692, 1642, 1601, 1517, 1460, 1388, 1216, 1167, 1114, 988, 847; 707, 665; HRMS (ESI) calcd for $[C_{29}H_{37}F_2N_3O_7 + H]^+$: 578.2672, found 578.2726.

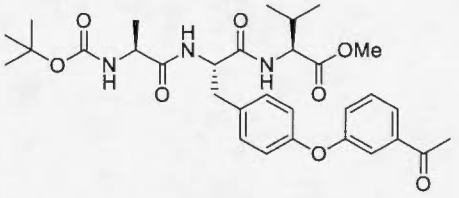
(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-(4-(3-vinylphenoxy)benzyl)-3-oxa-5,8,11-triazatridecan-13-oate (16j)



Method A was followed on a 0.0775 mmol scale starting from **12** and organobismuthine **6j**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16j** as a white solid (38.3 mg, 87%): mp 80-81 °C; R_f 0.53 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.8 Hz, 1H), 7.17-7.11 (m,

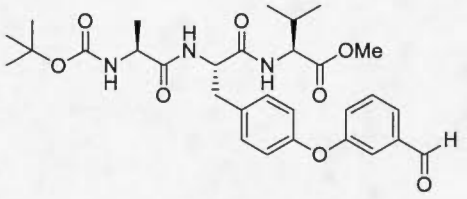
3H), 7.04 (t, *J* = 2.0 Hz, 1H), 6.93-6.84 (m, 4H), 6.65 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.64-6.54 (m, 1H), 5.70 (d, *J* = 17.5 Hz, 1H), 5.23 (d, *J* = 10.9 Hz, 1H), 5.11 (d, *J* = 7.2 Hz, 1H), 4.71 (q, *J* = 7.2 Hz, 1H), 4.44 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.18 (quint, *J* = 7.2 Hz, 1H), 3.69 (s, 3H), 3.03 (d, *J* = 6.9 Hz, 2H), 2.14-2.03 (m, 1H), 1.41 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.7, 157.5, 156.3, 155.5, 139.6, 136.4, 131.3, 130.8, 129.9, 121.4, 119.0, 118.3, 116.6, 114.8, 80.3, 57.4, 54.6, 52.2, 50.4, 37.6, 31.3, 28.5, 19.0, 18.5, 17.9; IR (neat) 3282, 3072, 2969, 2931, 1741, 1688, 1646, 1505, 1437, 1361, 1243, 1163, 1015, 931, 855, 786.8; HRMS (ESI) calcd for $[C_{31}H_{41}N_3O_7 + H]^+$: 568.3017, found 568.3030.

(6S,9S,12S)-Methyl 9-(4-(3-acetylphenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16k)



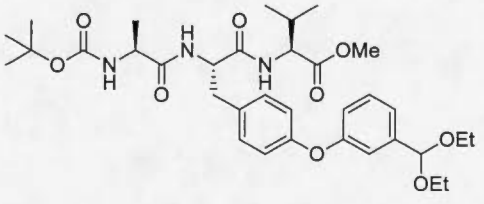
Method A was followed on a 0.0704 mmol scale starting from **12** and organobismuthine **6k**. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **16k** as an off-white solid (37.9 mg, 92%): mp 60-61 °C; R_f 0.33 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 2.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.19-7.16 (m, 2H), 6.92-6.89 (m, 2H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 8.6 Hz, 1H), 5.16 (d, *J* = 7.1 Hz, 1H), 4.70 (q, *J* = 7.2 Hz, 1H), 4.44 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.16 (quint, *J* = 6.9 Hz, 1H), 3.69 (s, 3H), 3.05 (d, *J* = 6.8 Hz, 2H), 2.56 (s, 3H), 2.15-2.04 (m, 1H), 1.39 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.6, 172.9, 171.9, 170.7, 157.9, 155.6, 138.9, 132.0, 131.0, 130.1, 123.3, 123.2, 119.4, 118.0, 80.3, 57.5, 54.5, 52.2, 50.4, 37.4, 31.3, 28.4, 26.9, 24.8, 19.0, 18.3, 17.9; IR (neat) 3293, 3068, 2969, 2923, 871, 2848, 1741, 1684, 1642, 1505, 1433, 1365, 1224, 1159, 1019, 897, 859, 783; HRMS (ESI) calcd for $[C_{31}H_{41}N_3O_8 + H]^+$: 584.2966, found 584.3011.

(6S,9S,12S)-Methyl 9-(4-(3-formylphenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16l)



Method B was followed on a 0.0752 mmol scale starting from **12** and organobismuthine **6l**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16l** as a white solid (42.7 mg, 99%): mp 65-66 °C; R_f 0.47 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.58 (td, *J* = 7.6, 1.3 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.41 (dd, *J* = 2.5, 1.4 Hz, 1H), 7.26 (ddd, *J* = 8.1, 2.7, 1.2 Hz, 1H), 7.23-7.18 (m, 2H), 6.96-6.91 (m, 2H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.54 (d, *J* = 8.6 Hz, 1H), 5.11 (d, *J* = 7.1 Hz, 1H), 4.70 (q, *J* = 7.1 Hz, 1H), 4.44 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.16 (quint, *J* = 6.9 Hz, 1H), 3.69 (s, 3H), 3.09-3.06 (m, 2H), 2.16-2.05 (m, 1H), 1.40 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 191.7, 172.9, 171.9, 170.6, 158.6, 155.6, 155.3, 138.2, 132.5, 131.1, 130.6, 124.9, 124.6, 119.8, 118.0, 80.4, 57.5, 54.6, 52.2, 50.4, 37.5, 31.3, 28.4, 19.0, 18.3, 17.9; IR (neat) 3285, 3081, 2966, 2925, 2852, 2729, 1740, 1695, 1650, 1503, 1450, 1360, 1250, 1164, 1013, 751; HRMS (ESI) calcd for $[C_{30}H_{39}N_3O_8 + H]^+$: 570.2810, found 570.2797.

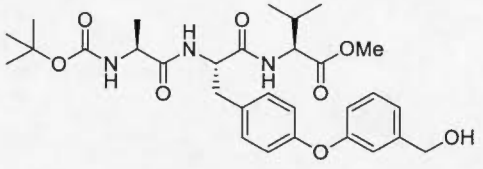
(6S,9S,12S)-Methyl 9-(4-(3-(diethoxymethyl)phenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16m)



Method B was followed on a 0.0649 mmol scale starting from **12** and organobismuthine **6m**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16m** as a white solid (39.0 mg, 93%): mp 53-54 °C; R_f 0.49 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.17-7.13 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 3H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 8.6 Hz, 1H), 5.45 (s, 1H), 5.04 (d, *J* = 7.1 Hz, 1H), 4.67 (q, *J* = 7.2 Hz, 1H), 4.42 (dd, *J* = 8.7, 5.3 Hz, 1H), 4.15 (quint, *J* = 5.9 Hz, 1H), 3.69 (s, 3H), 3.65-3.46 (m, 4H), 3.06-3.03 (m, 2H), 2.14-2.03 (m, 1H), 1.41 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 6H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8,

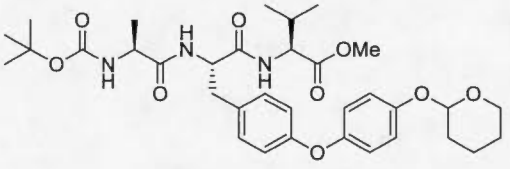
171.8, 170.6, 157.2, 156.4, 155.5, 141.4, 131.2, 130.8, 129.6, 121.7, 119.0, 118.6, 117.5, 101.1, 80.4, 61.2, 57.5, 54.6, 52.2, 50.4, 37.4, 31.3, 28.4, 19.0, 18.4, 17.9, 15.3; IR (neat) 3281, 3072, 2970, 2925, 2876, 1740, 1642, 1503, 1438, 1364, 1246, 1164, 1050, 903, 854, 780; HRMS (ESI) calcd for $[C_{34}H_{49}N_4O_4 + NH_4]^+$: 675.3838, found 675.3817.

(6S,9S,12S)-Methyl 9-(4-(3-(hydroxymethyl)phenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16n)



Method A was followed on a 0.107 mmol scale starting from **12** and organobismuthine **6n**. The crude product was purified on silica gel (70% EtOAc/hexanes) to afford **16n** as a white solid (56.5 mg, 93%): mp 73-74 °C; R_f 0.58 (100% EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.20 (m, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.98-6.94 (m, 2H), 6.92-6.85 (m, 3H), 6.73 (d, *J* = 6.9 Hz, 1H), 5.28-5.17 (m, 1H), 4.70 (q, *J* = 7.2 Hz, 1H), 4.63-4.62 (m, 2H), 4.43 (dd, *J* = 8.7, 5.3 Hz, 1H), 4.16-4.12 (m, 1H), 3.68 (s, 3H), 3.07-2.94 (m, 2H), 2.72 (s(br), 1H), 2.14-2.05 (m, 1H), 1.39 (s, 9H), 1.28 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.9, 172.0, 170.7, 157.9, 156.0, 155.5, 143.3, 131.5, 130.8, 129.9, 121.4, 119.5, 117.8, 116.7, 80.3, 64.8, 57.5, 54.6, 52.3, 50.3, 37.5, 31.3, 28.4, 19.0, 18.5, 18.0; IR (neat) 3281, 3072, 2962, 2920, 2852, 1737, 1642, 1502, 1441, 1365, 1247, 1163, 1019, 927, 855, 775, 692; HRMS (ESI) calcd for $[C_{30}H_{41}N_3O_8 + H]^+$: 572.2966, found 572.2981.

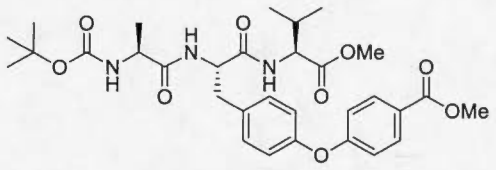
(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-(4-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenoxy)benzyl)-3-oxa-5,8,11-triazatridecan-13-oate (16o)



Method A was followed on a 0.107 mmol scale starting from **12** and organobismuthine **6o**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16o** as a light brown solid (57.5 mg, 82%): mp 79-80 °C; R_f 0.41 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.5 Hz, 2H), 7.02-6.98 (m, 2H), 6.94-6.90 (m, 2H), 6.85-6.83 (m, 3H), 6.54-6.51 (m, 1H), 5.33 (t, *J* = 3.4 Hz, 1H), 5.07 (d, *J* = 7.2 Hz, 1H), 4.66 (q, *J* = 7.1 Hz, 1H), 4.42 (dd, *J* = 8.5, 5.1 Hz, 1H), 4.16 (quint, *J* = 7.5 Hz, 1H), 3.96-3.88 (m, 1H),

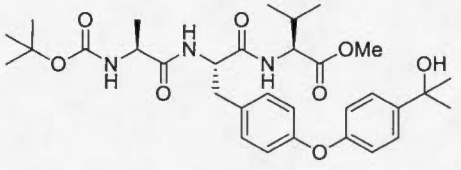
3.68 (s, 3H), 3.62-3.56 (m, 1H), 3.08-2.95 (m, 2H), 2.11-2.03 (m, 1H), 2.01-1.96 (m, 1H), 1.87-1.82 (m, 2H), 1.70-1.57 (m, 4H), 1.40 (s, 9H), 1.30 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.7, 157.4, 155.4, 153.4, 151.0, 130.6, 130.4, 120.6, 118.0, 117.8, 97.1, 80.3, 62.2, 57.5, 54.6, 52.2, 50.4, 37.4, 31.3, 30.5, 28.4, 25.3, 19.0, 18.5, 17.9; IR (neat) 3285, 3068, 2935, 2874, 1741, 1642, 1494, 1365, 1216, 1163, 1110, 1019, 962, 916, 874, 829; HRMS (ESI) calcd for $[C_{34}H_{47}N_3O_9 + H]^+$: 642.3385, found 642.3387.

(6S,9S,12S)-Methyl 12-isopropyl-9-(4-(4-(methoxycarbonyl)phenoxy)benzyl)-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16p)



Method A was followed on a 0.0604 mmol scale starting from **12** and organobismuthine **6p**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16p** as a white solid (33.4 mg, 92%): mp 79-80 °C; R_f 0.36 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98-7.94 (m, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 7.7 Hz, 4H), 6.93-6.88 (m, 1H), 6.70-6.52 (m, 1H), 5.12-5.10 (m, 1H), 4.72 (q, J = 6.2 Hz, 1H), 4.44 (dd, J = 8.4, 5.1 Hz, 1H), 4.18 (quint, J = 7.6 Hz, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 3.05 (d, J = 7.0 Hz, 2H), 2.15-2.04 (m, 1H), 1.40 (s, 9H), 1.31 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.9, 171.9, 170.6, 166.7, 161.8, 155.5, 154.7, 132.7, 131.8, 131.1, 124.6, 120.3, 117.3, 80.3, 57.4, 54.6, 52.3, 52.1, 50.3, 37.6, 31.3, 28.4, 19.0, 18.5, 17.9; IR (neat) 3289, 3076, 2969, 1718, 1646, 1498, 1433, 1239, 1159, 1099, 1015, 851, 764; HRMS (ESI) calcd for $[C_{31}H_{41}N_3O_9 + H]^+$: 600.2916, found 600.2914.

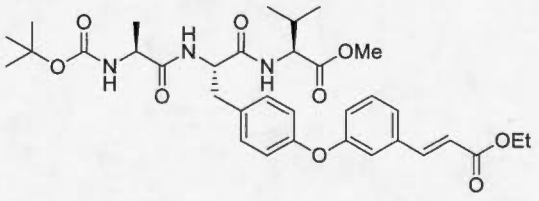
(6S,9S,12S)-Methyl 9-(4-(4-(2-hydroxypropan-2-yl)phenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16q)



Method B was followed on a 0.1065 mmol scale starting from **12** and organobismuthine **6q**. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **16q** as an off-white solid (56.6 mg, 93%): mp 78-79 °C; R_f 0.52 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44-7.41 (m, 2H), 7.16-7.13 (m,

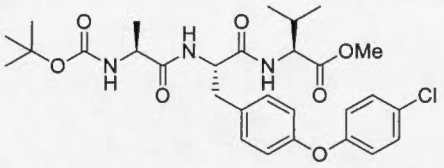
2H), 6.95-6.92 (m, 2H), 6.91-6.88 (m, 2H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 5.04 (d, *J* = 7.2 Hz, 1H), 4.67 (q, *J* = 7.1 Hz, 1H), 4.42 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.15 (quint, *J* = 7.4 Hz, 1H), 3.69 (s, 3H), 3.03 (d, *J* = 7.1 Hz, 2H), 2.14-2.03 (m, 1H), 2.00 (s(br), 1H), 1.57 (s, 6H), 1.41 (s, 9H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.6, 156.5, 155.9, 155.5, 144.2, 131.2, 130.7, 126.0, 119.0, 118.5, 80.4, 72.4, 57.5, 54.6, 52.3, 50.4, 37.4, 32.0, 31.3, 28.4, 19.0, 18.5, 17.9; IR (neat) 3289, 3068, 2969, 2931, 2871, 1741, 1692, 1646, 1498, 1361, 1235, 1163, 1015, 950, 855, 753; HRMS (ESI) calcd for $[C_{32}H_{45}N_3O_8 - H]^-$: 598.3136, found 598.3120.

(6S,9S,12S)-Methyl 9-(4-(3-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)phenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16r)



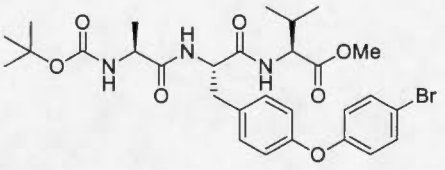
Method A was followed on a 0.0408 mmol scale starting from **12** and organobismuthine **6r**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **16r** as a white solid (23.6 mg, 89%): mp 68-69 °C; R_f 0.46 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 16.0 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.24-7.22 (m, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.15-7.13 (m, 1H), 7.02-6.98 (m, 1H), 6.93-6.90 (m, 2H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.54-6.42 (m, 1H), 6.37 (d, *J* = 16.0 Hz, 1H), 5.04 (d, *J* = 7.2 Hz, 1H), 4.68 (q, *J* = 7.1 Hz, 1H), 4.44 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.16 (quint, *J* = 6.8 Hz, 1H), 3.69 (s, 3H), 3.05 (d, *J* = 6.9 Hz, 2H), 2.15-2.06 (m, 1H), 1.41 (s, 9H), 1.33-1.28 (m, 6H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 171.8, 170.6, 166.9, 158.0, 155.8, 155.5, 144.0, 136.4, 131.8, 130.9, 130.3, 123.2, 120.5, 119.4, 119.2, 117.6, 80.4, 60.7, 57.4, 54.7, 52.3, 50.5, 37.5, 31.3, 28.4, 19.0, 18.4, 17.9, 14.4; IR (neat) 3289, 3068, 2969, 2931, 1707, 1642, 1498, 1441, 1365, 1232, 1163, 1023, 977, 855, 783; HRMS (ESI) calcd for $[C_{34}H_{45}N_3O_9 + H]^+$: 640.3229, found 640.3238.

(6S,9S,12S)-Methyl 9-(4-(4-chlorophenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16s)



Method A was followed on a 0.0749 mmol scale starting from **12** and organobismuthine **6s**. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **16s** as a white solid (42.3 mg, 98%): mp 151-152 °C; R_f 0.53 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2H), 7.19-7.16 (m, 2H), 6.94-6.87 (m, 4H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.42 (d, *J* = 8.6 Hz, 1H), 4.96 (d, *J* = 7.2 Hz, 1H), 4.66 (q, *J* = 7.1 Hz, 1H), 4.43 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.15 (quint, *J* = 6.9 Hz, 1H), 3.70 (s, 3H), 3.05 (d, *J* = 6.9 Hz, 2H), 2.17-2.04 (m, 1H), 1.42 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 172.8, 171.9, 170.5, 156.05, 156.03, 155.6, 131.7, 130.9, 129.8, 128.4, 120.1, 119.2, 80.5, 57.5, 54.7, 52.3, 50.4, 37.5, 31.3, 28.4, 19.0, 18.4, 17.9; IR (neat) 3277, 3072, 2958, 2921, 2852, 1740, 1687, 1642, 1499, 1479, 1360, 1234, 1164, 1086, 1001, 825, 756; HRMS (ESI) calcd for $[C_{29}H_{38}ClN_3O_7 + H]^+$: 576.2471, found 576.2486.

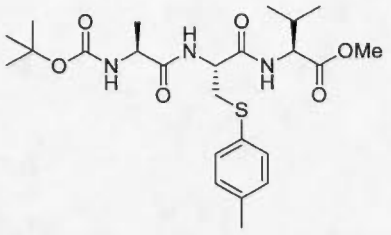
(6S,9S,12S)-Methyl 9-(4-(4-bromophenoxy)benzyl)-12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (16t)



Method A was followed on a 0.0749 mmol scale starting from **12** and organobismuthine **6t**. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **16t** as a white solid (40.9 mg, 88%): mp 158-159 °C; R_f 0.41 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43-7.38 (m, 2H), 7.20-7.15 (m, 2H), 6.91-6.85 (m, 4H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.45 (d, *J* = 8.6 Hz, 1H), 4.98 (d, *J* = 7.1 Hz, 1H), 4.67 (q, *J* = 7.1 Hz, 1H), 4.43 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.15 (quint, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 3.04 (d, *J* = 6.9 Hz, 2H), 2.15-2.04 (m, 1H), 1.41 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 172.8, 171.9, 170.6, 156.6, 155.9, 155.5, 132.8, 131.8, 130.9, 120.5, 119.3, 115.7, 80.4, 57.5, 54.6, 52.3, 50.4, 37.5, 31.3, 28.4, 19.0, 18.4, 17.9; IR (neat) 3281, 3077, 2962, 2917, 2852, 1740,

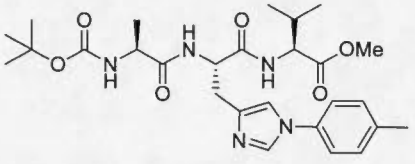
1687, 1642, 1499, 1479, 1364, 1234, 1164, 1070, 1005, 821, 747; HRMS (ESI) calcd for $[C_{29}H_{38}BrN_3O_7 + H]^+$: 620.1954, found 620.1966.

(6S,9R,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-((*p*-tolylthio)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (17)



Method B was followed on a 0.122 mmol scale starting from **13** and organobismuthine **6a**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **17** as an off-white solid (11.7 mg, 19%): mp 112-113 °C; R_f 0.56 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.95-6.75 (m, 2H), 4.76 (d, *J* = 4.4 Hz, 1H), 4.53-4.42 (m, 2H), 4.13 (quint, *J* = 7.3 Hz, 1H), 3.73 (s, 3H), 3.38 (dd, *J* = 14.0, 5.9 Hz, 1H), 3.18 (dd, *J* = 14.0, 6.7 Hz, 1H), 2.33 (s, 3H), 2.20-2.09 (m, 1H), 1.45 (s, 9H), 1.33 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 172.8, 171.9, 169.8, 155.5, 137.4, 131.0, 130.9, 130.2, 80.5, 57.7, 52.9, 52.3, 50.5, 36.1, 31.3, 28.5, 21.2, 19.0, 18.3, 18.0; IR (neat) 3289, 3072, 2966, 2921, 2872, 1744, 1646, 1511, 1454, 1360, 1246, 1205, 1164, 1021, 858, 805; HRMS (ESI) calcd for $[C_{24}H_{37}N_3O_6S - H]^-$: 494.2330, found 494.2323.

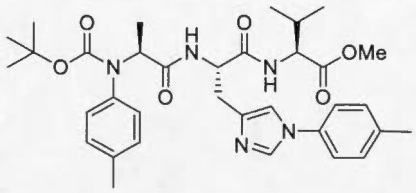
(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-((1-(*p*-tolyl)-*1H*-imidazol-4-yl)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (18a)



Method B was followed on a 0.0974 mmol scale starting from **14** and organobismuthine **6a**. The crude product was purified on silica gel (5% MeOH/CH_2Cl_2) to afford **18a** as an off-white solid (5.5 mg, 11%): mp 54-55 °C; R_f 0.40 (100% EtOAc); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.14 (s(br), 1H), 7.93-7.89 (m, 1H), 7.55-7.45 (m, 1H), 7.31-7.27 (m, 2H), 7.25-7.19 (m, 2H), 7.13 (d, *J* = 4.0 Hz, 1H), 5.25 (s(br), 1H), 4.87-4.75 (m, 1H), 4.40 (dd, *J* = 8.4, 5.2 Hz, 1H), 4.30-4.20 (m, 1H), 3.68 (s, 3H), 3.30-3.17 (m, 1H), 3.17-3.06 (m, 1H), 2.40 (s, 3H), 2.11-2.08 (m, 1H), 1.44-1.42 (m, 3H), 1.41 (s, 9H), 0.85-0.74 (m, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 173.2, 172.0, 170.9, 155.6, 138.4, 137.9, 134.33, 134.26, 130.7, 121.6, 117.1, 79.9, 57.7, 53.5, 52.2, 50.7,

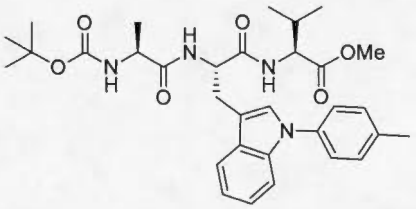
30.9, 29.3, 28.5, 21.1, 19.04, 19.01, 17.8; IR (neat) 3315, 3032, 2965, 2928, 2874, 2855, 1741, 1686, 1512, 1458, 1368, 1320, 1255, 1206, 1166, 1073, 1026, 909, 858, 817, 757, 734, 524; HRMS (ESI) calcd for $[C_{27}H_{39}N_5O_6 + H]^+$: 530.2973, found 530.2989.

(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-5-(*p*-tolyl)-9-((1-(*p*-tolyl)-*1H*-imidazol-4-yl)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (18b)



Method B was followed on a 0.0974 mmol scale starting from **14** and organobismuthine **6a**. The crude product was purified on silica gel (5% MeOH/CH_2Cl_2) to afford **18b** as a white solid (27.9 mg, 46%): mp 65-66 °C; R_f 0.64 (100% EtOAc); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.17-8.09 (m, 1H), 8.09 (d, *J* = 4.5 Hz, 1H), 7.92 (d, *J* = 6.2 Hz, 1H), 7.31-7.26 (m, 4H), 7.22 (s, 1H), 7.13-7.10 (m, 2H), 7.08-7.07 (m, 2H), 5.02 (m, 1H), 4.54 (q, *J* = 7.1 Hz, 1H), 4.40 (dd, *J* = 8.0, 5.5 Hz, 1H), 3.68 (s, 3H), 3.40-3.30 (m, 1H), 3.16 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H), 2.22-2.17 (m, 1H), 1.33 (s, 9H), 1.31-1.30 (m, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 172.4, 172.1, 171.0, 155.0, 138.2, 136.7, 133.9, 130.7, 130.2, 129.5, 129.4, 128.3, 125.7, 121.8, 117.7, 80.9, 58.2, 58.1, 53.2, 52.1, 30.7, 29.9, 28.4, 21.17, 21.16, 19.2, 18.1, 15.6; IR (neat) 3315, 3032, 2965, 2928, 2874, 2855, 1741, 1686, 1512, 1458, 1368, 1320, 1255, 1206, 1166, 1073, 1026, 909, 858, 817, 757, 734, 524; HRMS (ESI) calcd for $[C_{34}H_{45}N_5O_6 + H]^+$: 620.3443, found 620.3397.

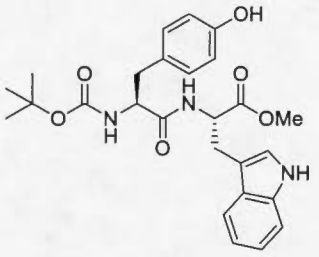
(6S,9S,12S)-Methyl 12-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-9-((1-(*p*-tolyl)-*1H*-indol-3-yl)methyl)-3-oxa-5,8,11-triazatridecan-13-oate (19)



Method B was followed on a 0.102 mmol scale starting from **15** and organobismuthine **6a**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **19** as a yellow oil (14.0 mg, 24%): R_f 0.46 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 6.9 Hz, 1H), 7.50 (dd, *J* = 6.6, 1.5 Hz, 1H),

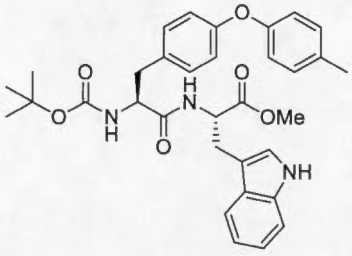
7.36-7.33 (m, 2H), 7.29-7.26 (m, 2H), 7.23-7.14 (m, 3H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 6.9 Hz, 1H), 5.04 (d, *J* = 7.1 Hz, 1H), 4.89 (q, *J* = 7.8 Hz, 1H), 4.37 (dd, *J* = 8.4, 5.2 Hz, 1H), 4.10 (quint, *J* = 6.8 Hz, 1H), 3.62 (s, 3H), 3.37 (dd, *J* = 14.5, 5.7 Hz, 1H), 3.23 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.41 (s, 3H), 1.97-1.91 (m, 1H), 1.38 (s, 9H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.68 (d, *J* = 7.7 Hz, 3H), 0.66 (d, *J* = 8.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.0, 172.0, 171.2, 155.5, 137.1, 136.3, 136.2, 130.2, 128.7, 127.0, 124.1, 122.7, 120.4, 119.2, 111.3, 110.8, 80.2, 57.6, 53.7, 52.1, 50.5, 30.8, 28.3, 27.8, 21.1, 18.7, 18.2, 17.8; IR (neat) 3358, 3048, 2970, 2925, 2872, 1740, 1695, 1650, 1516, 1458, 1360, 1246, 1164, 1017, 825, 731; HRMS (ESI) calcd for $[C_{32}H_{42}N_4O_6 + H]^+$: 579.3177, found 579.3155.

(S)-Methyl 2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)-3-(*1H*-indol-3-yl)propanoate (20)



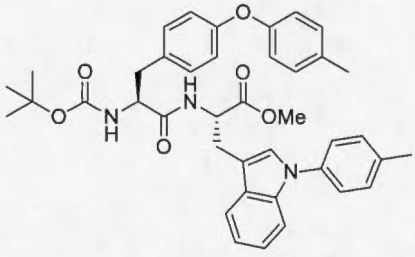
Boc-Tyr-OH (608 mg, 2.16 mmol), H-Trp-OMe•HCl (471 mg, 2.16 mmol) and HCTU (981 mg, 2.37 mmol) were dissolved in CH_2Cl_2 (22 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (1.32 mL, 7.55 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 X 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 50 mL), sat. aq. NaCl (2 X 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **20** as a white solid (739.1 mg, 71%): mp 88-89 °C; R_f 0.39 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.45 (s(br), 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.99-6.82 (m, 1H), 6.79 (s, 1H), 6.61 (d, *J* = 8.1 Hz, 2H), 6.42-6.15 (m, 1H), 5.30-4.92 (m, 1H), 4.92-4.66 (m, 1H), 4.64-3.82 (m, 1H), 3.52 (s, 3H), 3.21 (d, *J* = 4.6 Hz, 2H), 3.00-2.63 (m, 2H), 1.40 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.0, 171.5, 155.7, 155.4, 136.2, 130.5, 127.8, 127.5, 123.3, 122.3, 119.7, 118.4, 115.7, 111.6, 109.3, 80.6, 56.1, 53.2, 52.5, 37.9, 28.3, 27.6; IR (neat) 3323, 3057, 2977, 2928, 1658, 1513, 1437, 1365, 1228, 1159, 1011, 840, 737; HRMS (ESI) calcd for $[C_{26}H_{31}N_3O_6 + H]^+$: 482.2286, found 482.2295.

(S)-Methyl 2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(*p*-tolyloxy)phenyl)propanamido)-3-(*1H*-indol-3-yl)propanoate (21)



Method B was followed on a 0.106 mmol scale starting from **20** and organobismuthine **6a**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **21** as an off-white solid (49.0 mg, 82%): mp 58-59 °C; R_f 0.48 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (s(br), 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.13-7.05 (m, 5H), 6.89-6.84 (m, 5H), 6.39 (d, *J* = 7.6 Hz, 1H), 5.00-4.98 (m, 1H), 4.87 (q, *J* = 5.4 Hz, 1H), 4.32-4.31 (m, 1H), 3.64 (s, 3H), 3.27-3.25 (m, 2H), 2.98-2.96 (m, 2H), 2.32 (s, 3H), 1.38 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.9, 171.0, 156.9, 155.4, 154.8, 136.2, 133.0, 131.0, 130.7, 130.3, 127.6, 123.1, 122.3, 119.8, 119.1, 118.5, 111.5, 109.8, 80.2, 55.9, 53.1, 52.5, 37.8, 28.3, 27.8, 20.8; IR (neat) 3330, 3052, 2921, 2856, 1736, 1659, 1503, 1454, 1364, 1234, 1160, 1107, 1017, 813, 743; HRMS (ESI) calcd for $[C_{33}H_{37}N_3O_6 + H]^+$: 572.2755, found 572.2803.

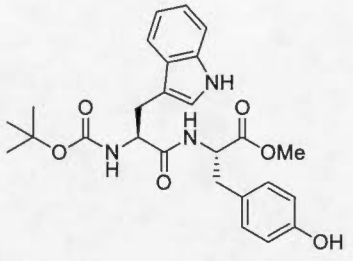
(S)-Methyl 2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(*p*-tolyloxy)phenyl)propanamido)-3-(1-(*p*-tolyl)-*1H*-indol-3-yl)propanoate (22)



Method B was followed on a 0.105 mmol scale starting from **20** and organobismuthine **6a**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **22** as an orange-pink solid (5.5 mg, 8%): mp 134-135 °C; R_f 0.69 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.36-7.28 (m, 4H), 7.20 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.15-7.06 (m, 6H), 6.85 (dd, *J* = 8.4, 1.4 Hz, 4H), 6.43 (d, J = 7.7 Hz, 1H), 4.94-4.88 (m, 2H), 4.31-4.29 (m, 1H), 3.67 (s, 3H), 3.31 (d, *J* = 5.4 Hz, 2H), 2.98 (d, *J* = 6.3 Hz, 2H), 2.43 (s, 3H), 2.32 (s, 3H), 1.36 (s, 9H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 171.8, 170.9, 156.9, 155.3, 154.7, 137.1, 136.4, 136.2, 133.0, 130.9, 130.7, 130.33, 130.26, 128.9, 126.9, 124.3, 122.7, 120.3,

119.2, 118.9, 118.5, 110.9, 110.6, 80.2, 55.9, 53.0, 52.5, 37.7, 28.3, 27.8, 21.2, 20.8; IR (neat) 3326, 3036, 2921, 2852, 1740, 1691, 1654, 1516, 1458, 1385, 1238, 1168, 1013, 821, 735, 629; HRMS (ESI) calcd for $[C_{40}H_{43}N_3O_6 + H]^+$: 662.3225, found 662.3228.

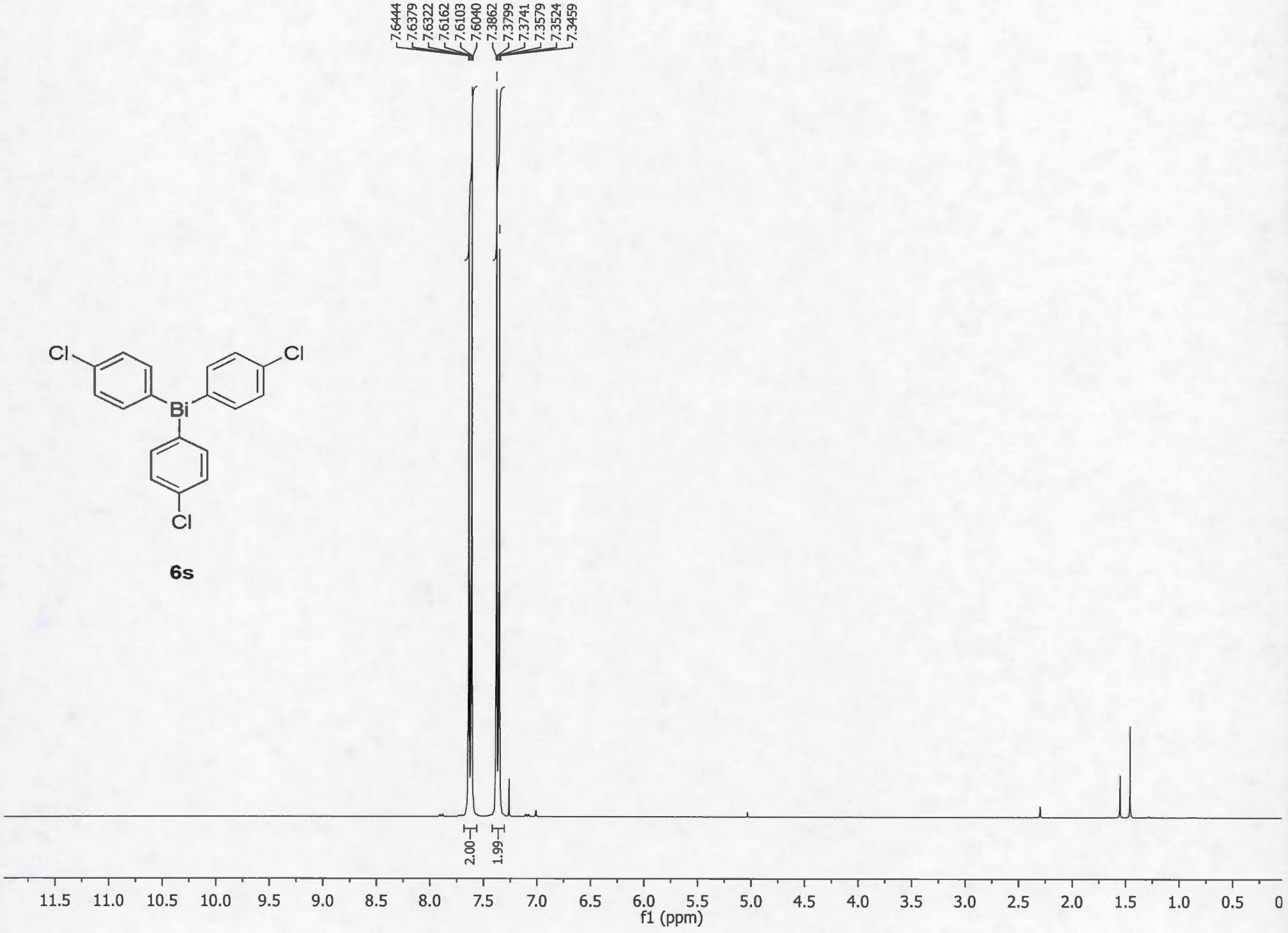
(S)-Methyl 2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(*1H*-indol-3-yl)propanamido)-3-(4-hydroxyphenyl)propanoate (23)



Boc-Trp-OH (927 mg, 3.05 mmol), H-Tyr-OMe•HCl (705 mg, 3.05 mmol) and HCTU (1.385 g, 3.35 mmol) were dissolved in CH_2Cl_2 (30 mL) in a round bottom flask with a stir bar. The flask was chased with argon, the mixture was cooled to 0°C in an ice bath and DiPEA (1.86 mL, 10.66 mmol) was added dropwise. The reaction mixture was warmed up to room temperature and was stirred for 16 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 X 100 mL), sat. aq. NaCl (2 X 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel (60% EtOAc/hexanes) to afford **23** as a white solid (1.105 g, 74%): mp 105-106°C °C; R_f 0.49 (60% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (s(br), 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.36 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.82 (s, 1H), 6.68-6.55 (m, 4H), 6.44 (d, *J* = 7.7 Hz, 1H), 5.26 (s(br), 1H), 4.71 (q, *J* = 6.5 Hz, 1H), 4.58-4.27 (m, 1H), 3.59 (s, 3H), 3.38-3.18 (m, 1H), 3.11 (dd, *J* = 14.5, 6.8 Hz, 1H), 2.91-2.78 (m, 2H), 1.41 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.7, 171.6, 155.8, 155.5, 136.3, 130.4, 127.6, 127.0, 123.5, 122.3, 119.8, 118.8, 115.6, 111.4, 110.1, 80.6, 55.5, 53.5, 52.4, 37.2, 28.4, 28.2; IR (neat) 3327, 3053, 2977, 2931, 1658, 1509, 1433, 1365, 1224, 1159, 1007, 844, 737; HRMS (ESI) calcd for $[C_{26}H_{31}N_3O_6 + H]^+$: 482.2286, found 482.2285.

(S)-Methyl 2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(*1H*-indol-3-yl)propanamido)-3-(4-(*p*-tolyloxy)phenyl)propanoate (24)

Method A was followed on a 0.104 mmol scale starting from **23** and organobismuthine **6a**. The crude product was purified on silica gel (40% EtOAc/hexanes) to afford **24** as an off-white solid (41.4 mg, 70%): mp 51-52 °C; R_f 0.37 (4% MeOH/CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (s(br), 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.16 (dt, *J* = 7.1, 1.2 Hz, 1H), 7.14-7.05 (m, 3H), 7.00 (s, 1H), 6.90-6.83 (m, 2H), 6.73 (s, 4H), 6.31 (d, *J* = 7.4 Hz, 1H), 5.32-5.00 (m, 1H), 4.71 (q, *J* = 5.5 Hz, 1H), 4.54-4.31 (m, 1H), 3.61 (s, 3H), 3.39-3.21 (m, 1H), 3.14 (dd, *J* = 14.5, 7.0 Hz, 1H) 2.90 (dd, *J* = 5.6, 2.2 Hz, 2H), 2.34 (s, 3H), 1.42 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.4, 157.0, 155.5, 154.6, 136.4, 133.1, 130.47, 130.36, 130.0, 127.6, 123.5, 122.4, 119.9, 119.3, 119.0, 118.3, 111.3, 110.5, 80.3, 55.3, 53.4, 52.3, 37.2, 28.4, 20.8; IR (neat) 3370, 3064, 2961, 2924, 2857, 1743, 1662, 1504, 1458, 1441, 1368, 1239, 1172, 1101, 1014, 874, 874, 740; HRMS (ESI) calcd for $[C_{33}H_{37}N_3O_6 + H]^+$: 572.2755, found 572.2783.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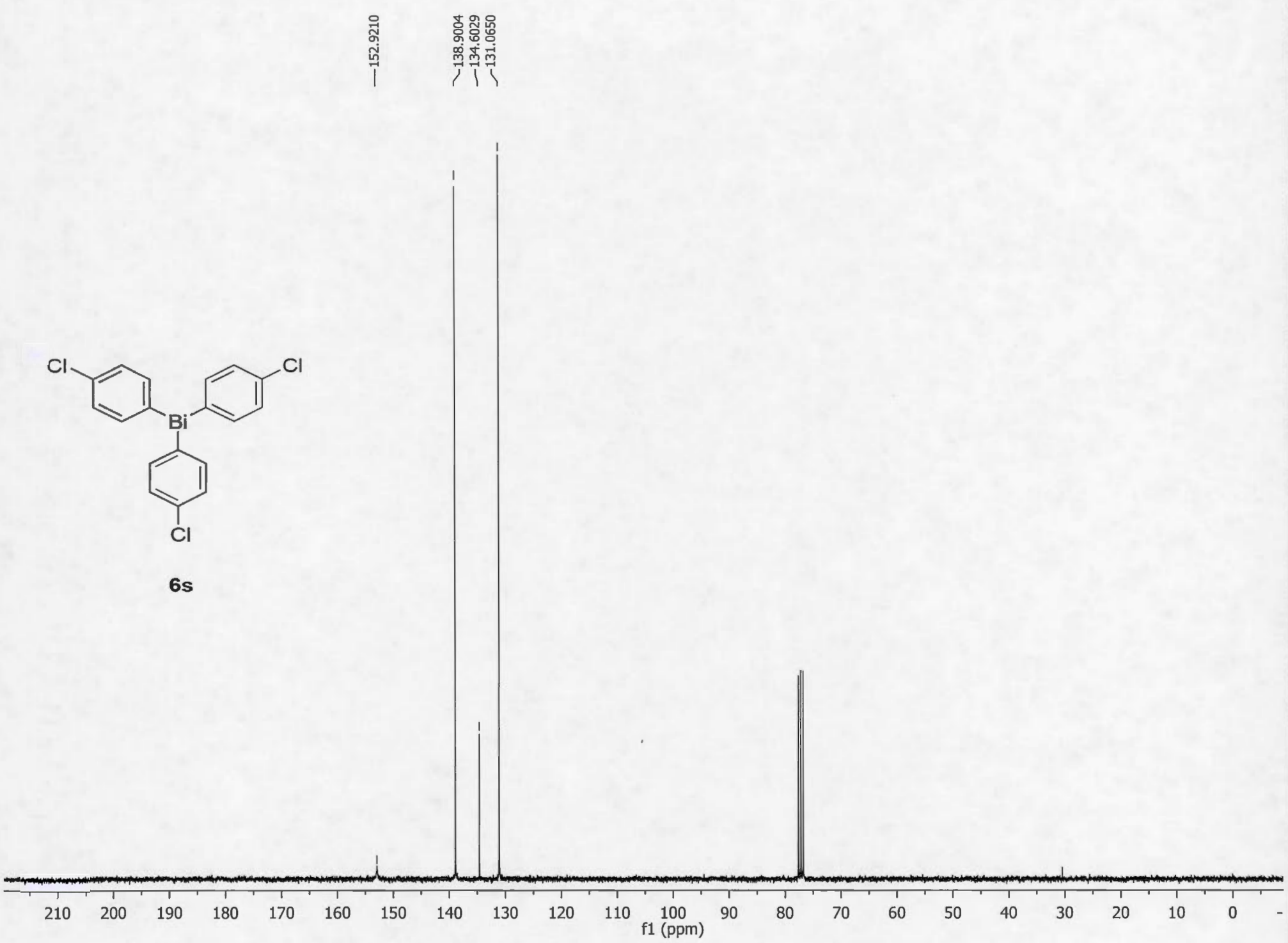
7.6379
7.6322
7.6162
7.6103
7.6040
7.3862
7.3799
7.3741
7.3579
7.3524
7.3459
Cl
Cl
Bi
Cl
2.00
1.99
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

6s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131.0650
Cl
Cl
Bi
Cl
6s
210
200
190
180
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160
150
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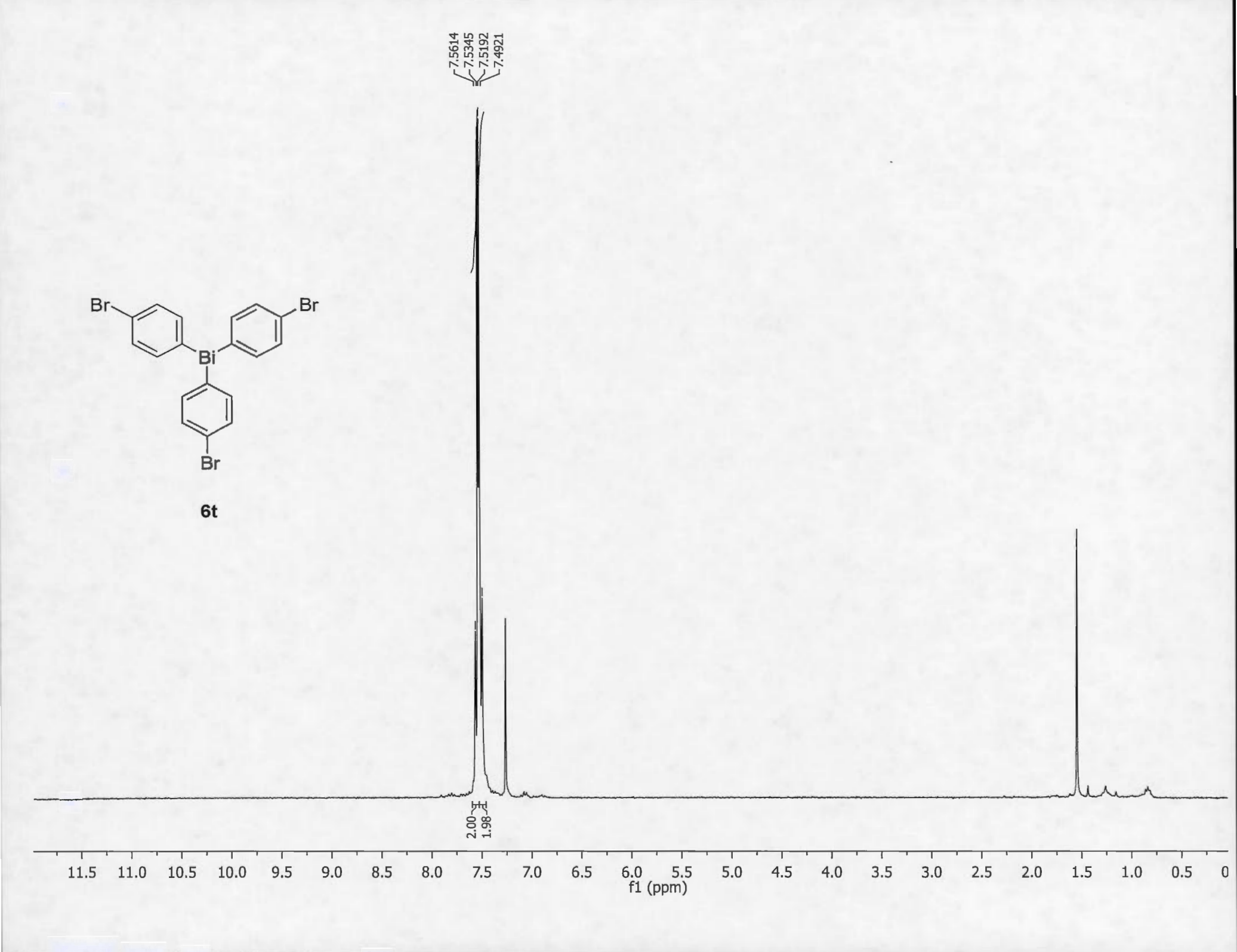
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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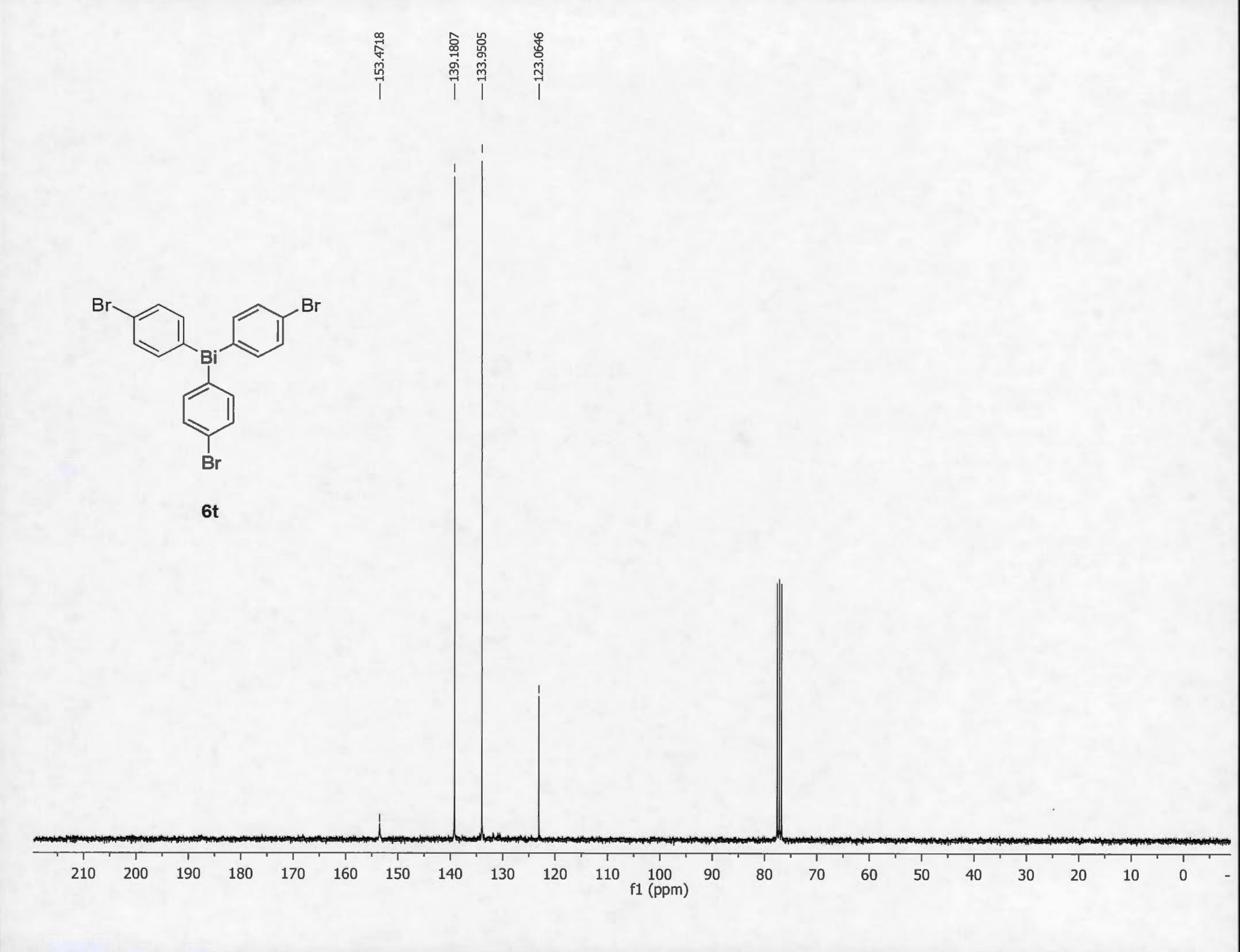
7.5192
7.4921
Br
Br
Bi
Br
6t
2.00
1.98
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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Br
Br
Bi
Br
6t
210
200
190
180
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160
150
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130
120
110
100
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70
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50
40
30
20
10
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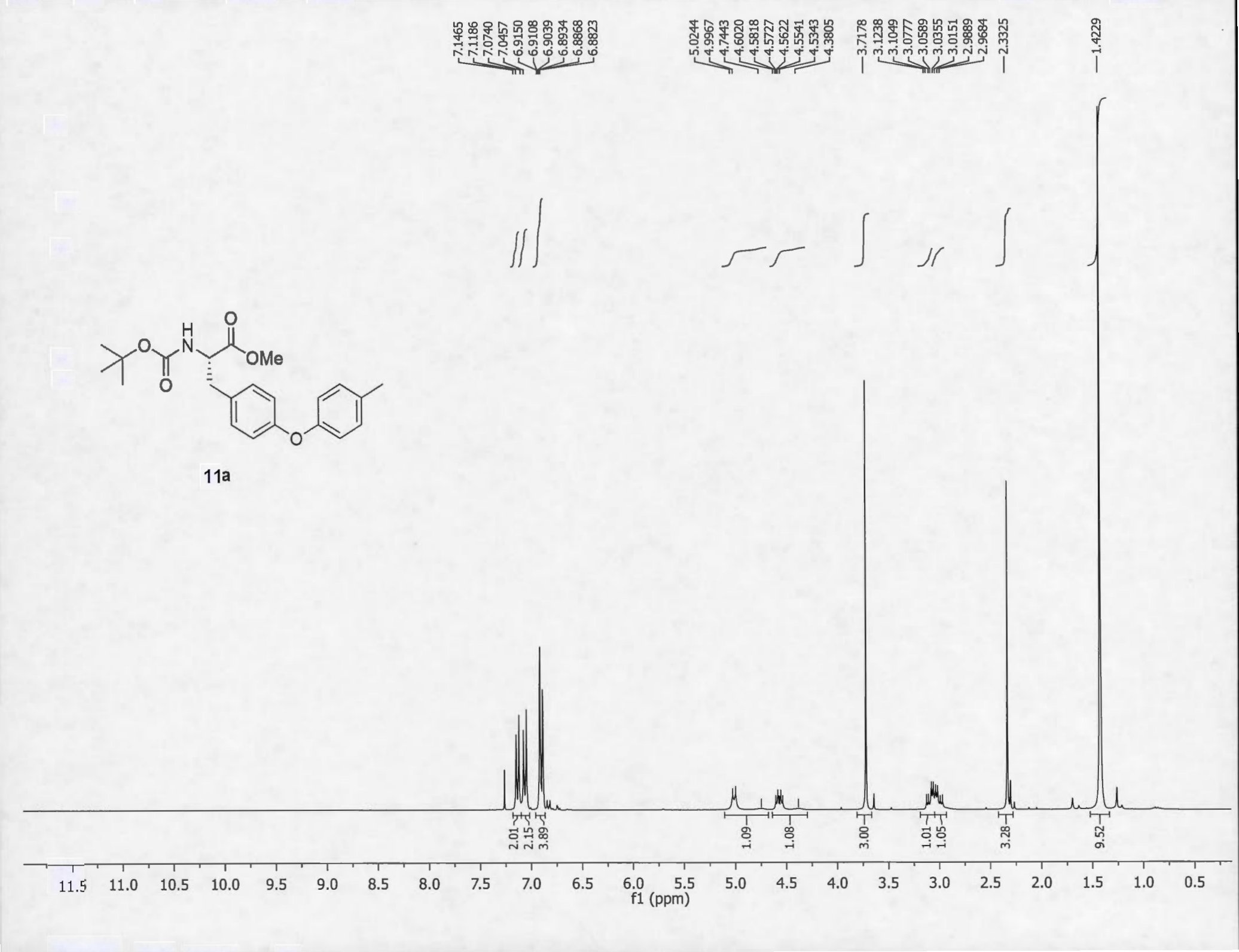
f1 (ppm)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7.0740
7.0457
6.9150
6.9108
6.9039
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6.8868
6.8823
5.0244
4.9967
4.7443
4.6020
4.5818
4.5727
4.5622
4.5541
4.5343
4.3805
3.7178
3.1238
3.1049
3.0777
3.0589
3.0355
3.0151
2.9889
2.9684
2.3325
1.4229
O
H
N
O
O
O
OMe
O
11a
2.01
2.15
3.89
1.09
1.08
3.00
1.01
1.05
3.28
9.52
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

11a
OMe
172.4407
157.0284
155.1788
154.6905
133.0931
130.6144
130.4097
130.3455
119.2629
118.4031
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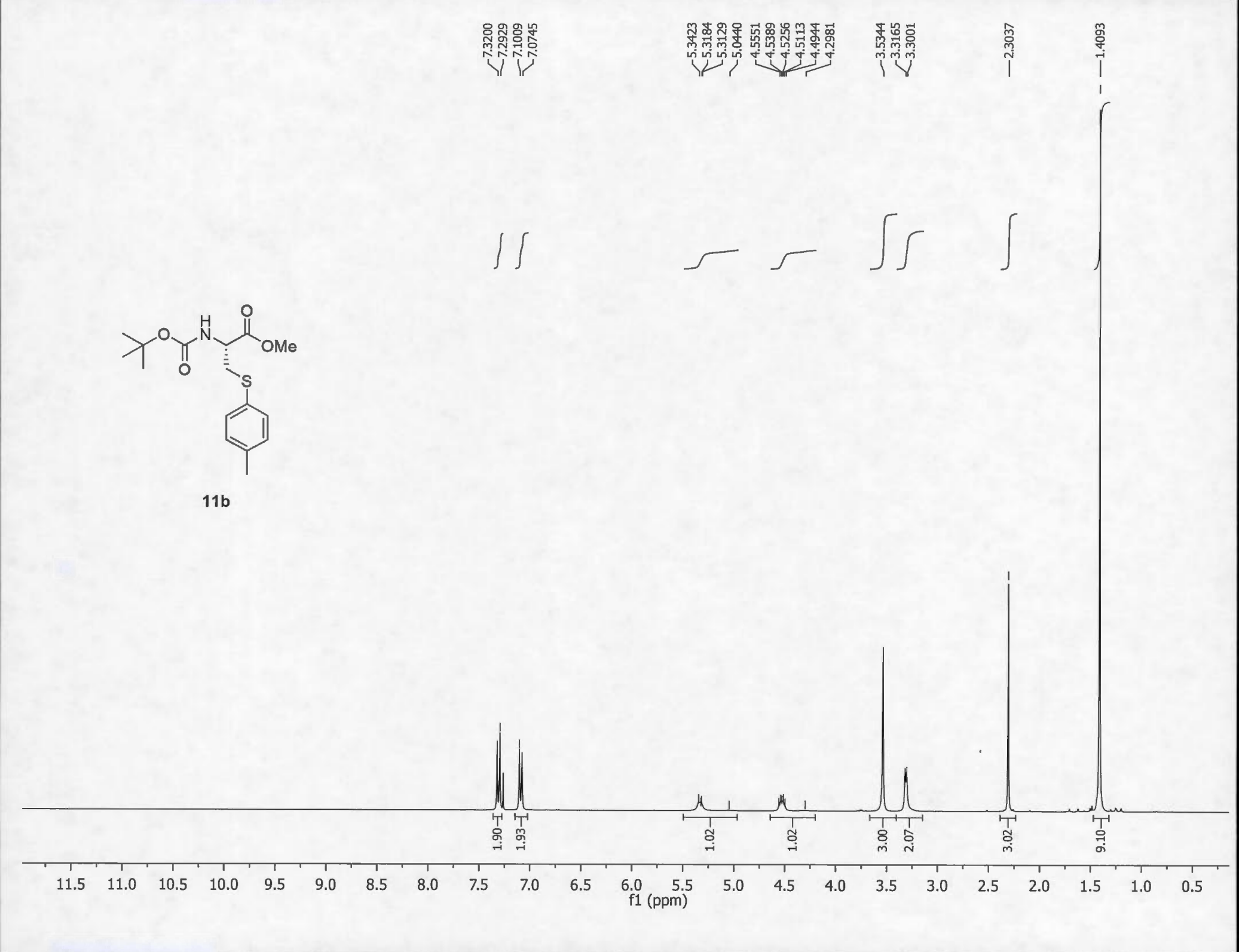
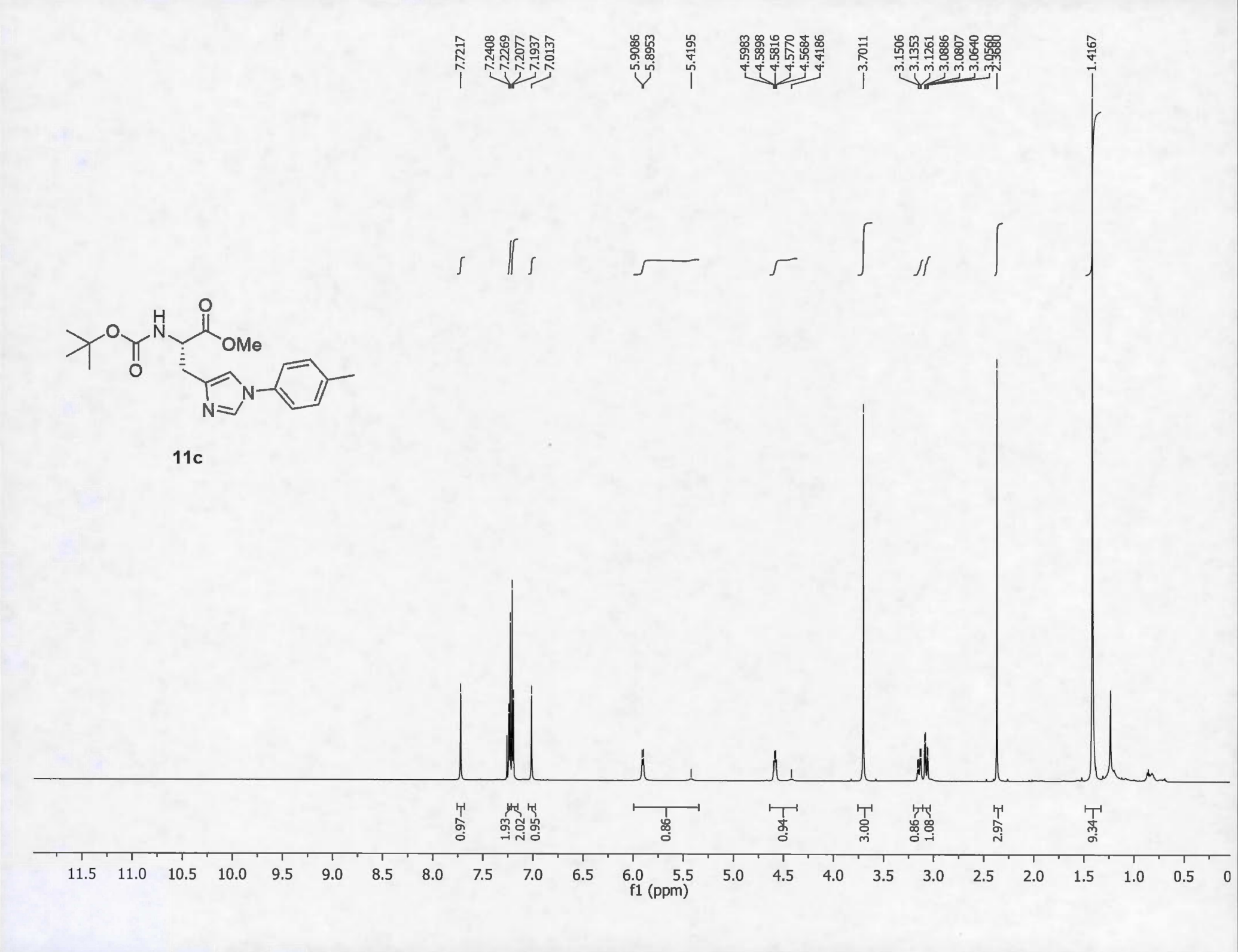
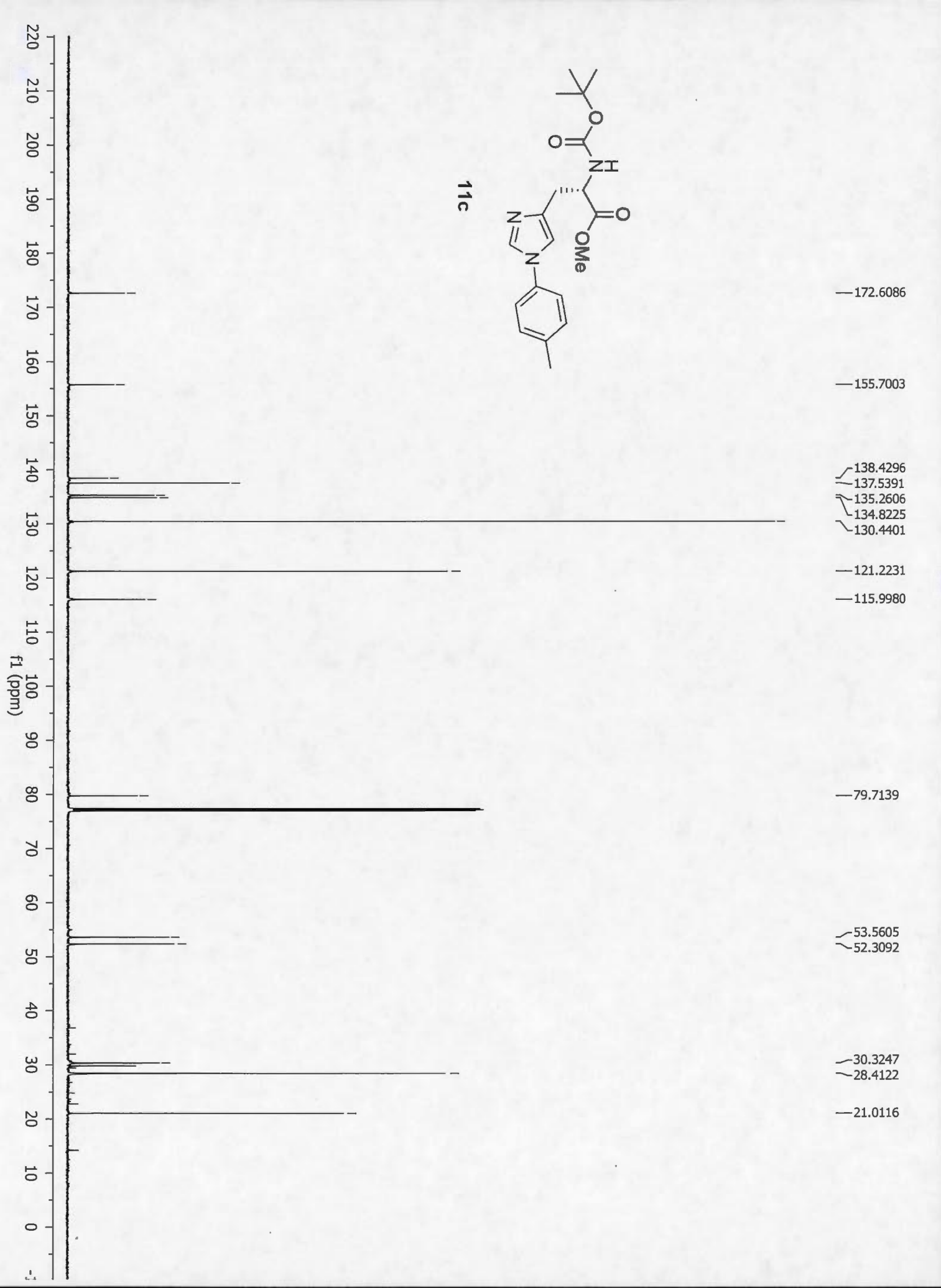
52.3455
37.7532
28.4124
20.8269
f1 (ppm)

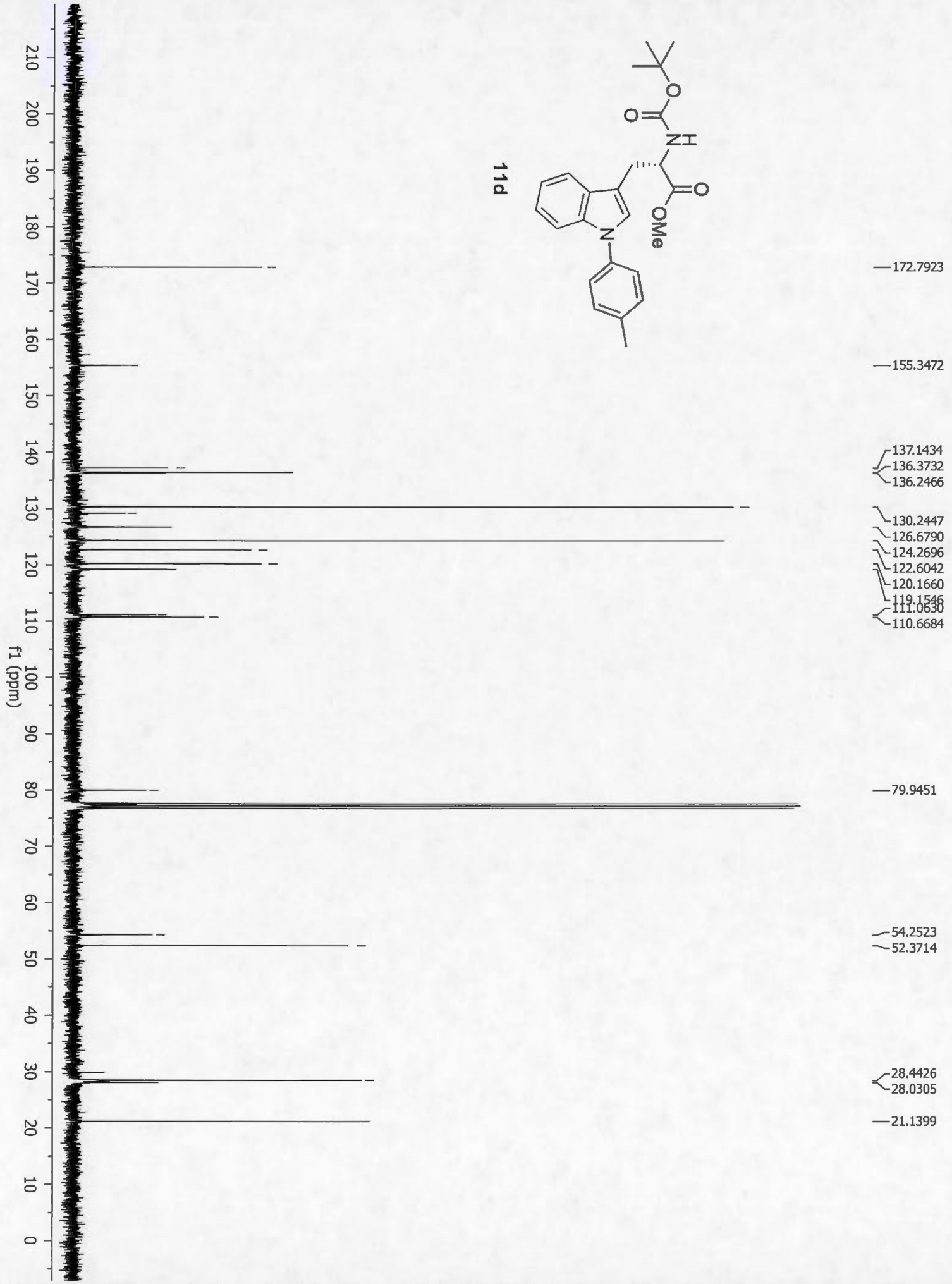

7.3200
7.2929
7.1009
7.0745
5.3423
5.3184
5.3129
5.0440
4.5551
4.5389
4.5256
4.5113
4.4944
4.2981
3.5344
3.3165
3.3001
2.3037
1.4093
H
N
O
O
O
OMe
S
11b
1.90
1.93
1.02
1.02
3.00
2.07
3.02
9.10
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

11b
O
O
NH
S
O
OMe
171.1804
155.0493
137.3566
131.8552
131.0272
129.8876
80.0972
53.3810
52.3803
37.9039
28.3609
21.1405
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

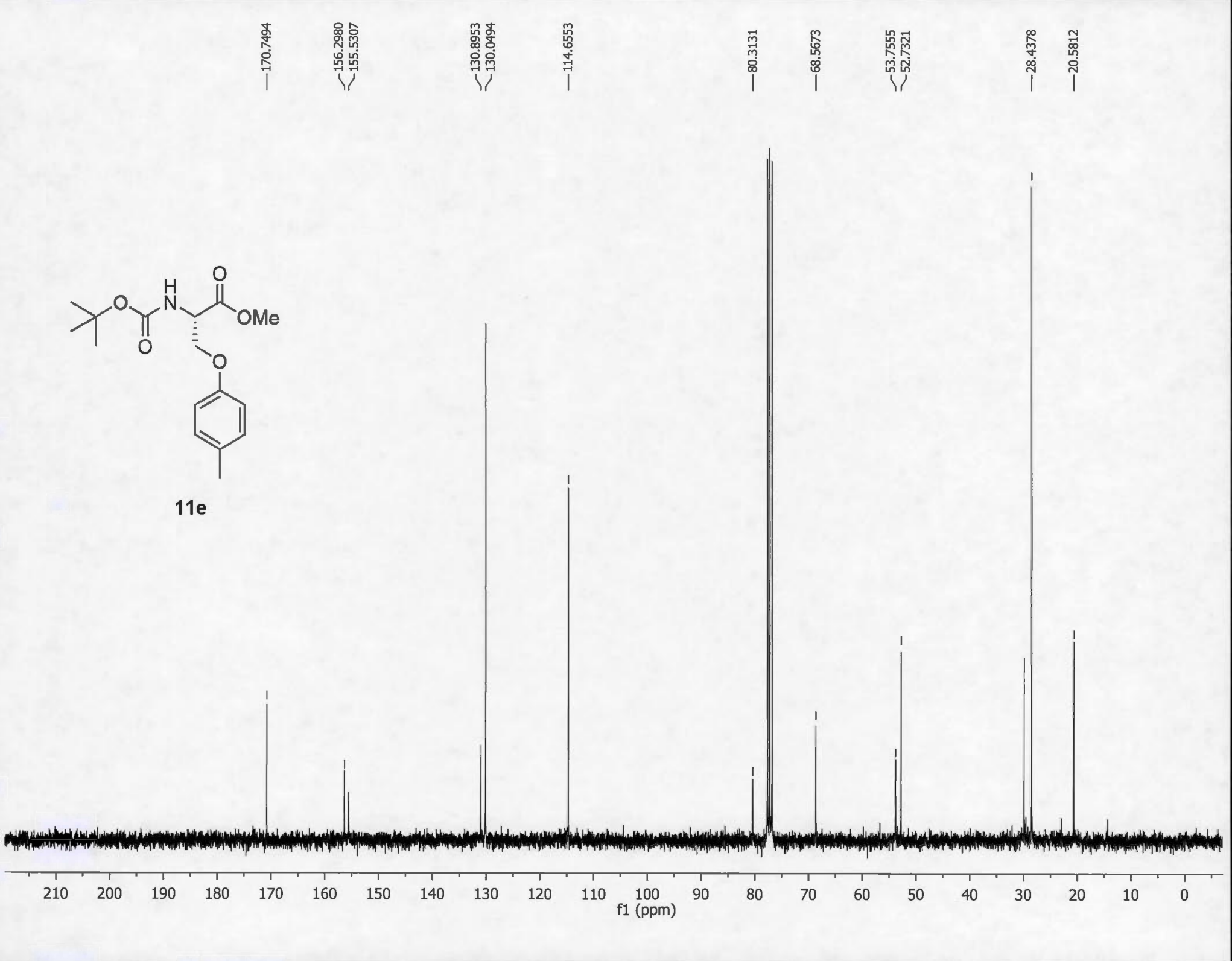

7.7217
7.2408
7.2269
7.2077
7.1937
7.0137
5.9086
5.8953
5.4195
4.5983
4.5898
4.5816
4.5770
4.5684
4.4186
3.7011
3.1506
3.1353
3.1261
3.0886
3.0807
3.0640
2.9680
1.4167
OMe
11c
0.97
1.93
2.02
0.95
0.86
0.94
3.00
0.86
1.08
2.97
9.34
f1 (ppm)


11c
OMe
172.6086
155.7003
138.4296
137.5391
135.2606
134.8225
130.4401
121.2231
115.9980
79.7139
53.5605
52.3092
30.3247
28.4122
21.0116
f1 (ppm)

11d
OMe
f1 (ppm)
1.00
0.98
4.01
1.97
1.07
1.00
1.00
3.00
1.84
3.01
8.04
7.6278
7.6037
7.5248
7.4996
7.3776
7.3707
7.3493
7.3252
7.2970
7.2593
7.2503
7.2459
7.2265
7.2228
7.1990
7.1950
7.1722
7.1698
7.1386
5.1670
5.1392
4.8870
4.7479
4.7285
4.7143
4.7034
4.6838
4.5406
3.7199
3.3691
3.3540
2.4404
1.4484


11d
O
O
NH
O
OMe
N
172.7923
155.3472
137.1434
136.3732
136.2466
130.2447
126.6790
124.2696
122.6042
120.1660
119.1546
111.0630
110.6684
79.9451
54.2523
52.3714
28.4426
28.0305
21.1399
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

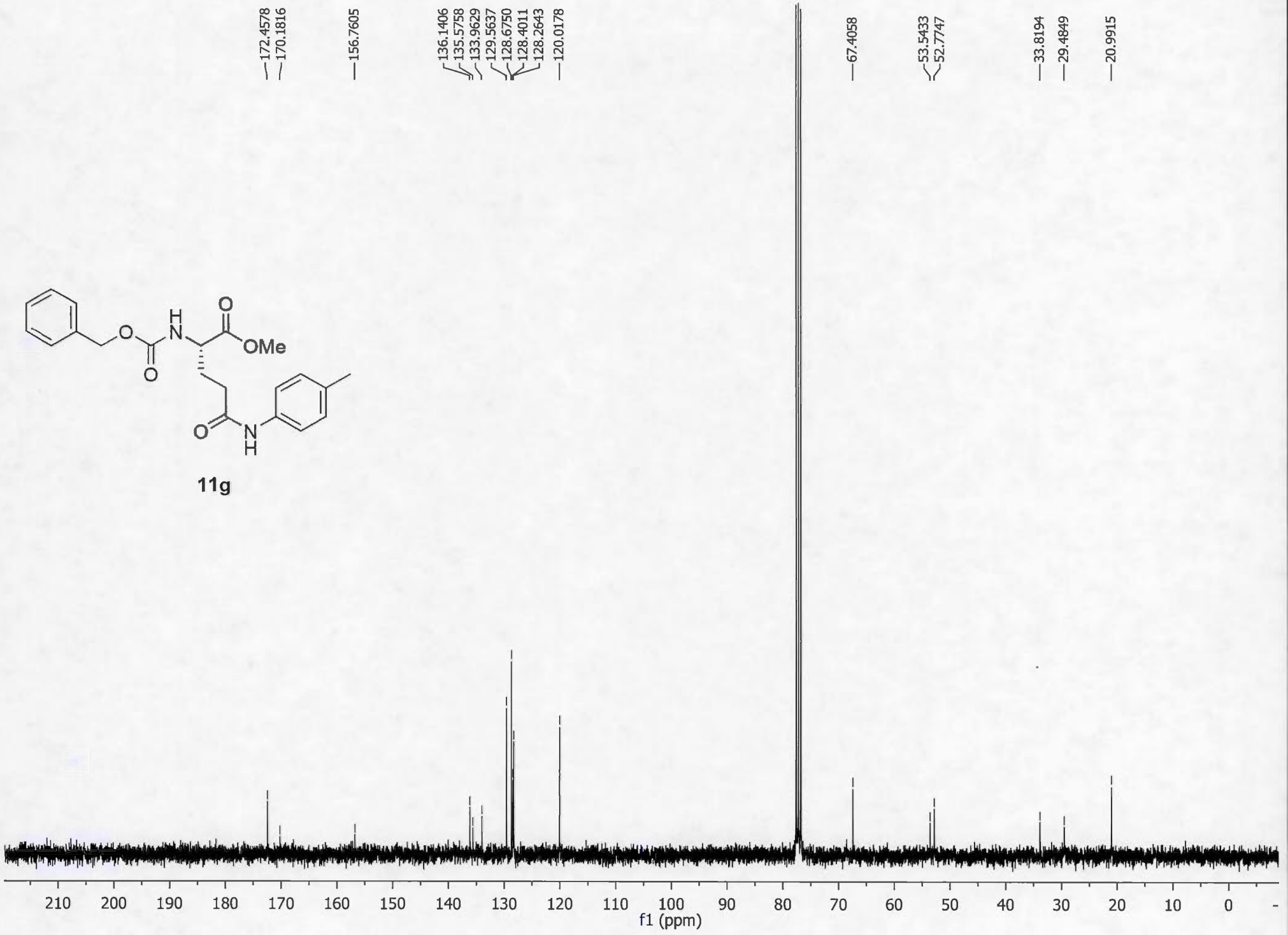
11e
O
O
NH
O
O
OMe
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
1.94
1.98
0.85
0.92
1.01
1.04
3.00
3.08
9.50
7.0844
7.0780
7.0639
7.0565
6.7848
6.7778
6.7634
6.7565
5.5255
5.4961
4.6591
4.6295
4.3826
4.3728
4.3516
4.3418
4.1865
4.1760
4.1558
4.1451
3.7591
2.2794
1.4586

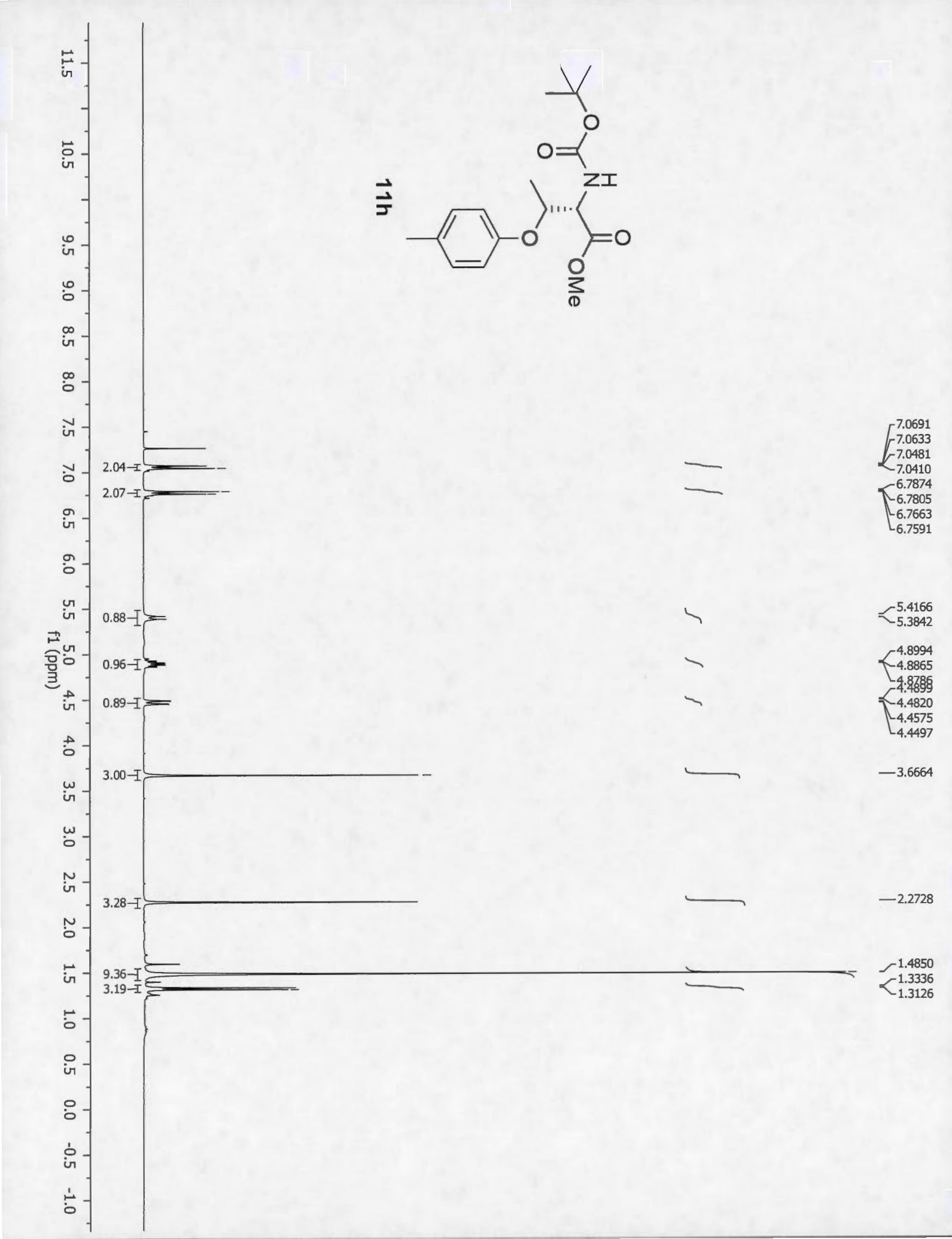

170.7494
156.2980
155.5307
130.8953
130.0494
114.6553
80.3131
68.5673
53.7555
52.7321
28.4378
20.5812
OMe
11e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

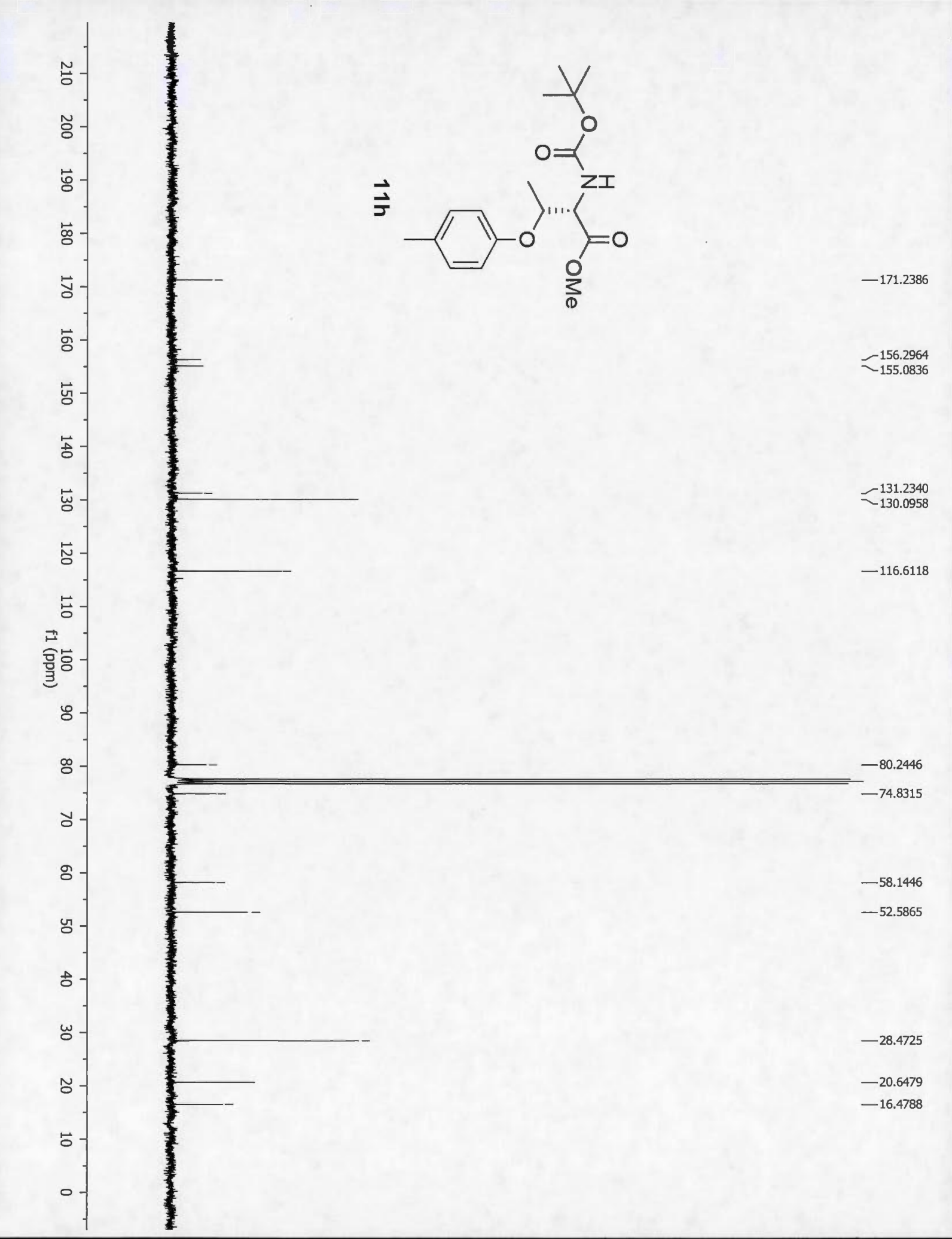
11f
OMe
f1 (ppm)
4.48
1.79
1.80
0.87
1.98
0.98
3.00
1.91
2.77
1.07
1.02
2.07
2.07
7.3807
7.3746
7.3632
7.3503
7.3410
7.0029
6.9760
6.5370
6.5101
5.3592
5.3313
5.1253
4.4441
4.4184
4.4007
4.3747
3.7444
3.1052
3.0824
3.0591
2.2445
1.8930
1.8768
1.8624
1.8451
1.8275
1.7078
1.6802
1.6588
1.6478
1.6339
1.6239
1.6017
1.4846

11f
173.0166
156.0007
146.1378
136.3150
129.8182
128.6468
128.3205
128.2406
126.5500
113.0233
67.1487
53.8166
52.5052
44.0843
32.6907
29.1508
22.9459
20.4752
f1 (ppm)

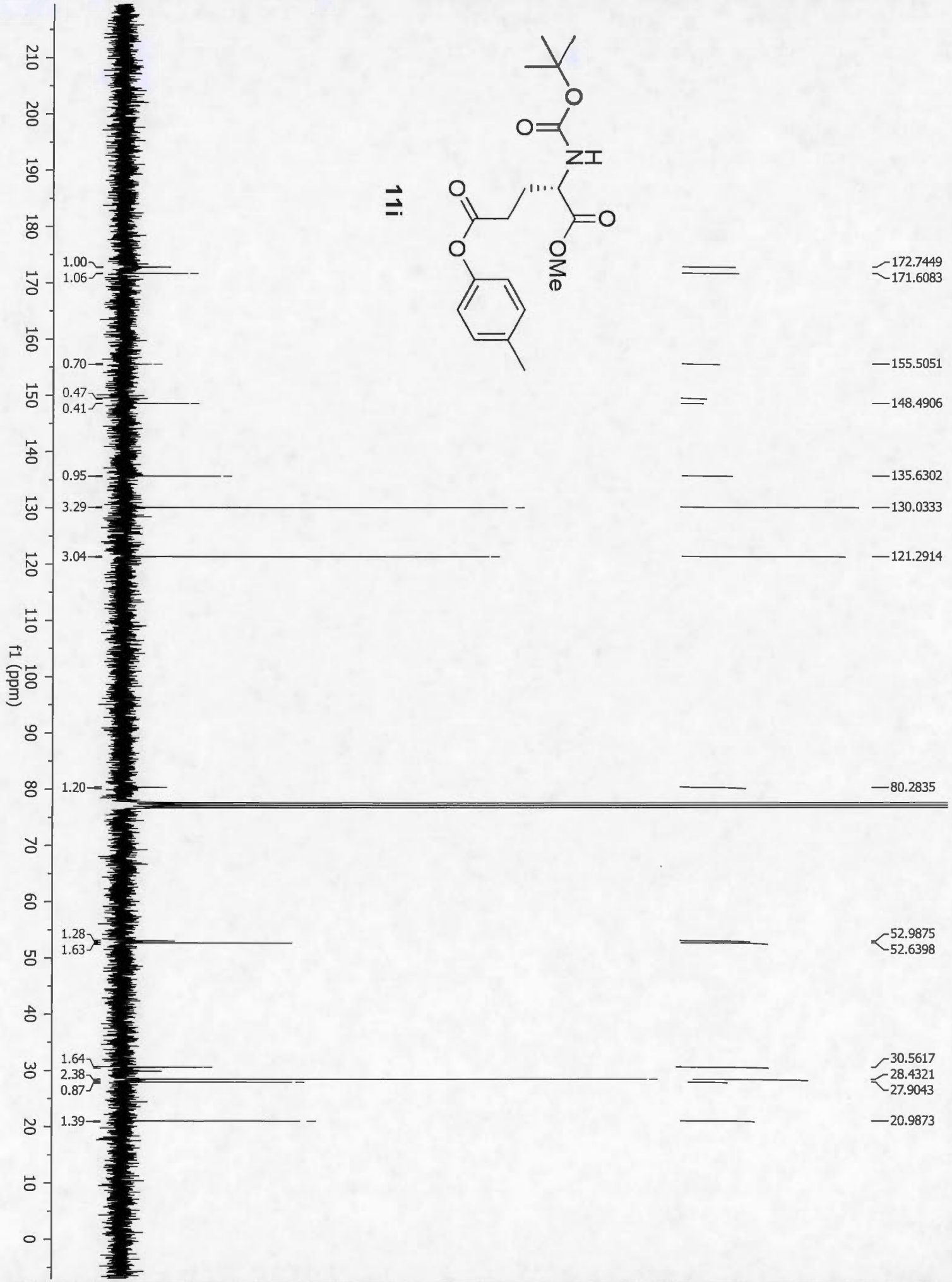
11g
OMe
f1 (ppm)
0.81
1.77
4.79
2.00
1.05
2.06
1.04
3.00
2.11
2.99
0.89
1.31
8.1385
7.4229
7.3967
7.3133
7.0957
7.0691
5.8313
5.8045
5.0829
4.4084
4.3999
4.3844
4.3723
3.7011
2.4017
2.3810
2.2943
2.0412
2.0124
1.9911
1.9665


172.4578
170.1816
156.7605
136.1406
135.5758
133.9629
129.5637
128.6750
128.4011
128.2643
120.0178
67.4058
53.5433
52.7747
33.8194
29.4849
20.9915
OMe
11g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

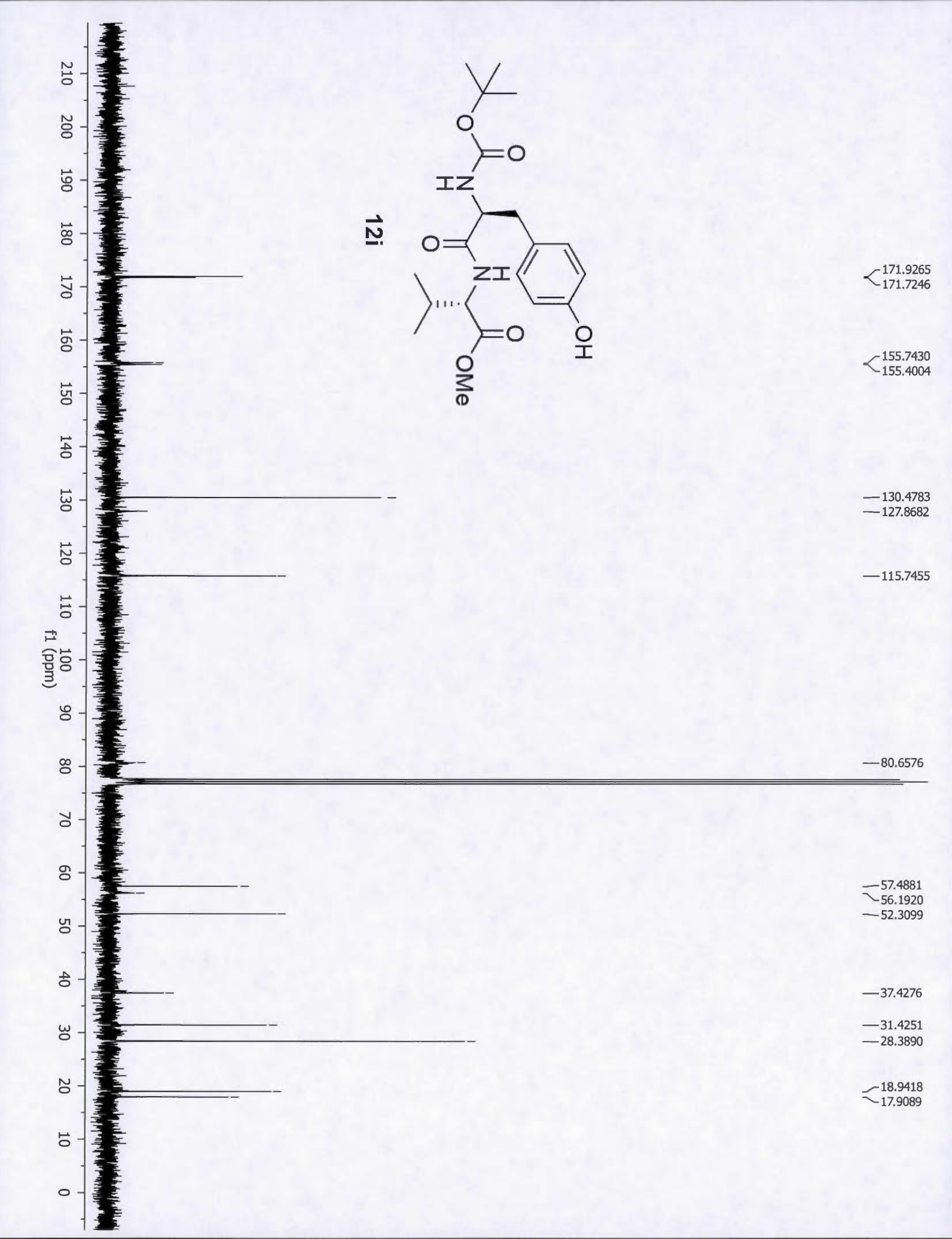

11h
OMe
f1 (ppm)
2.04
2.07
0.88
0.96
0.89
3.00
3.28
9.36
3.19
7.0691
7.0633
7.0481
7.0410
6.7874
6.7805
6.7663
6.7591
5.4166
5.3842
4.8994
4.8865
4.8786
4.4899
4.4820
4.4575
4.4497
3.6664
2.2728
1.4850
1.3336
1.3126

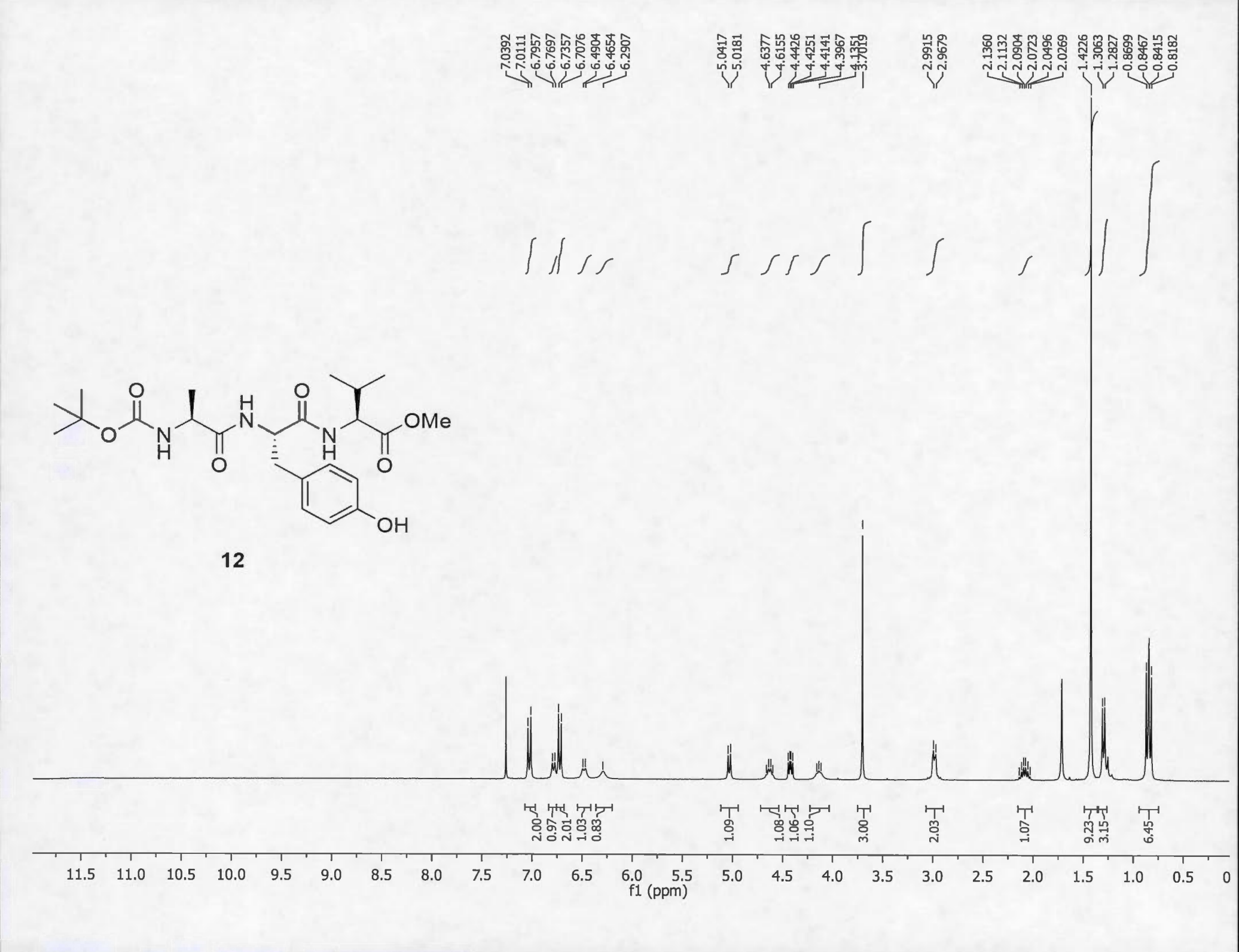

11h
171.2386
156.2964
155.0836
131.2340
130.0958
116.6118
80.2446
74.8315
58.1446
52.5865
28.4725
20.6479
16.4788
f1 (ppm)

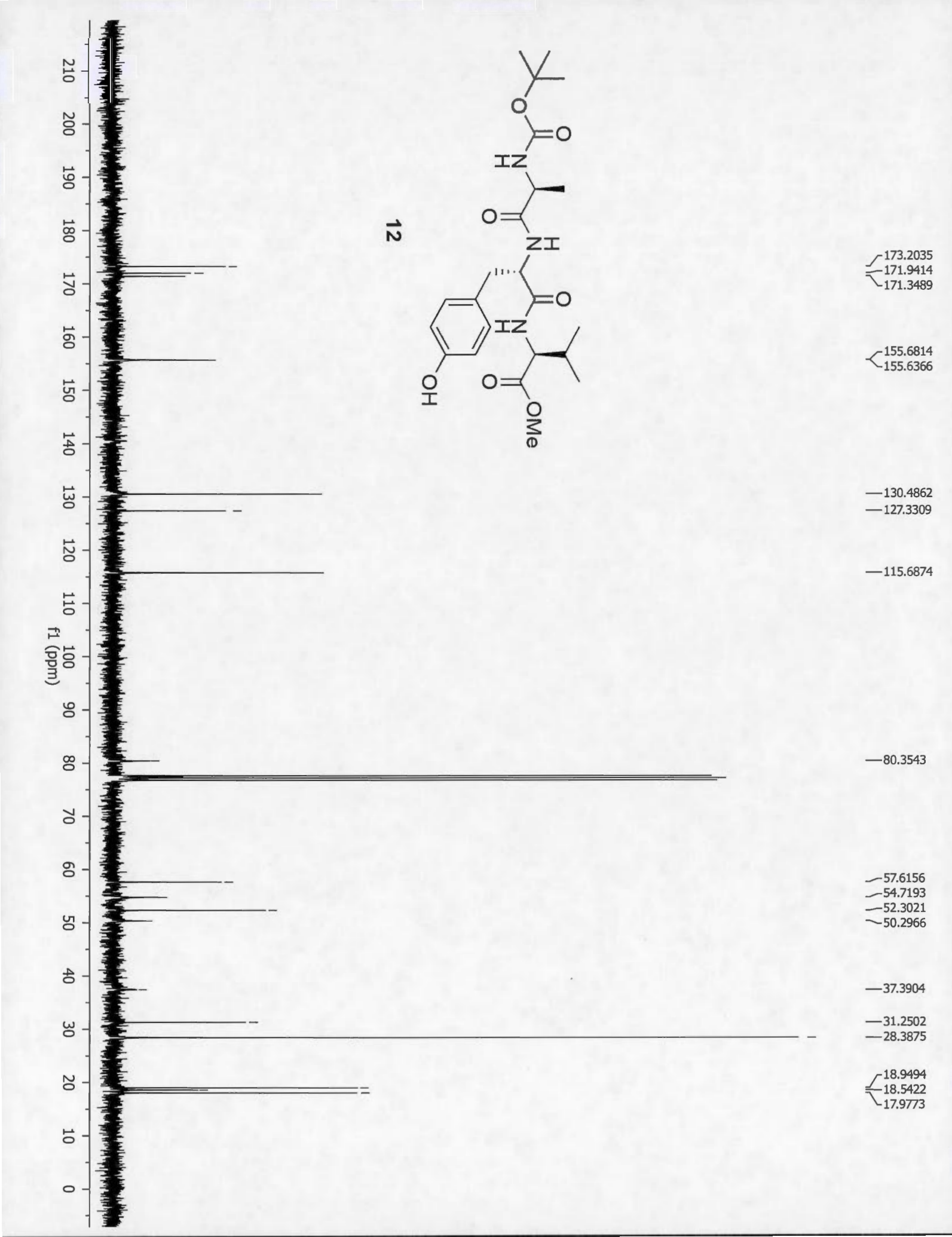
11i
OMe
NH
O
O
O
O
O
O
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
1.87
1.85
1.03
0.98
3.00
1.96
3.04
1.02
1.17
9.32
7.1748
7.1475
6.9799
6.9518
5.1668
5.1406
5.1196
4.4292
4.4114
4.3866
3.7584
2.6828
2.6647
2.6573
2.6409
2.6320
2.6169
2.3357
2.2848
2.2644
2.1212
2.0939
2.0721
2.0470
2.0231
1.4518

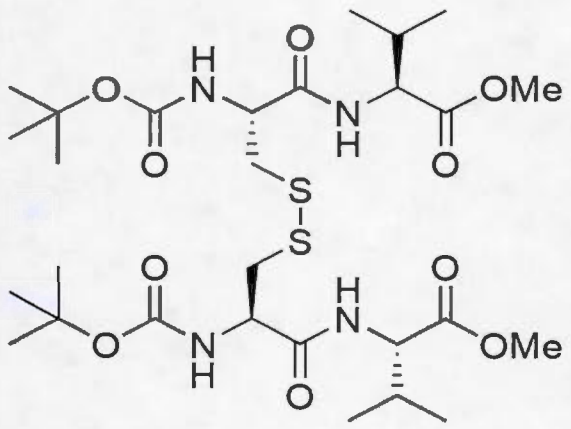

11i
NH
OMe
1.00
1.06
0.70
0.47
0.41
0.95
3.29
3.04
1.20
1.28
1.63
1.64
2.38
0.87
1.39
172.7449
171.6083
155.5051
148.4906
135.6302
130.0333
121.2914
80.2835
52.9875
52.6398
30.5617
28.4321
27.9043
20.9873
f1 (ppm)

12i
O
O
HN
O
NH
O
OMe
OH
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
1.95
0.71
2.01
0.93
0.98
1.02
0.98
3.00
1.94
1.15
8.39
6.01
7.0244
6.9981
6.8824
6.7376
6.7109
6.4737
5.1366
4.4459
4.3051
4.2777
3.6828
2.9755
2.9524
2.1205
2.0985
2.0759
2.0527
1.4170
0.8803
0.8555
0.8306


12i
171.9265
171.7246
155.7430
155.4004
130.4783
127.8682
115.7455
80.6576
57.4881
56.1920
52.3099
37.4276
31.4251
28.3890
18.9418
17.9089
f1 (ppm)

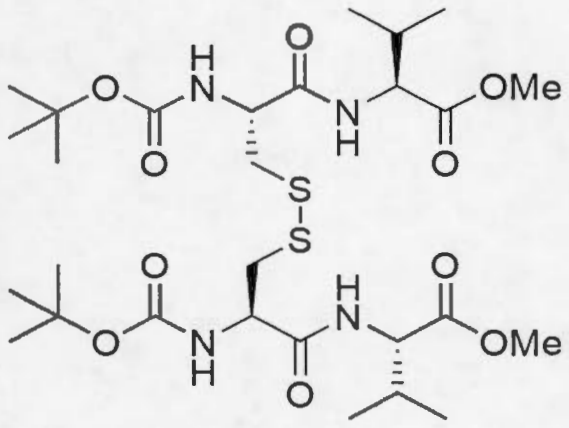

7.0392
7.0111
6.7957
6.7697
6.7357
6.7076
6.4904
6.4654
6.2907
5.0417
5.0181
4.6377
4.6155
4.4426
4.4251
4.4141
4.3967
4.1351
3.7019
2.9915
2.9679
2.1360
2.1132
2.0904
2.0723
2.0496
2.0269
1.4226
1.3063
1.2827
0.8699
0.8467
0.8415
0.8182
OMe
OH
12
2.00
0.97
2.01
1.03
0.83
1.09
1.08
1.06
1.10
3.00
2.03
1.07
9.23
3.15
6.45
f1 (ppm)


12
OH
OMe
173.2035
171.9414
171.3489
155.6814
155.6366
130.4862
127.3309
115.6874
80.3543
57.6156
54.7193
52.3021
50.2966
37.3904
31.2502
28.3875
18.9494
18.5422
17.9773
f1 (ppm)



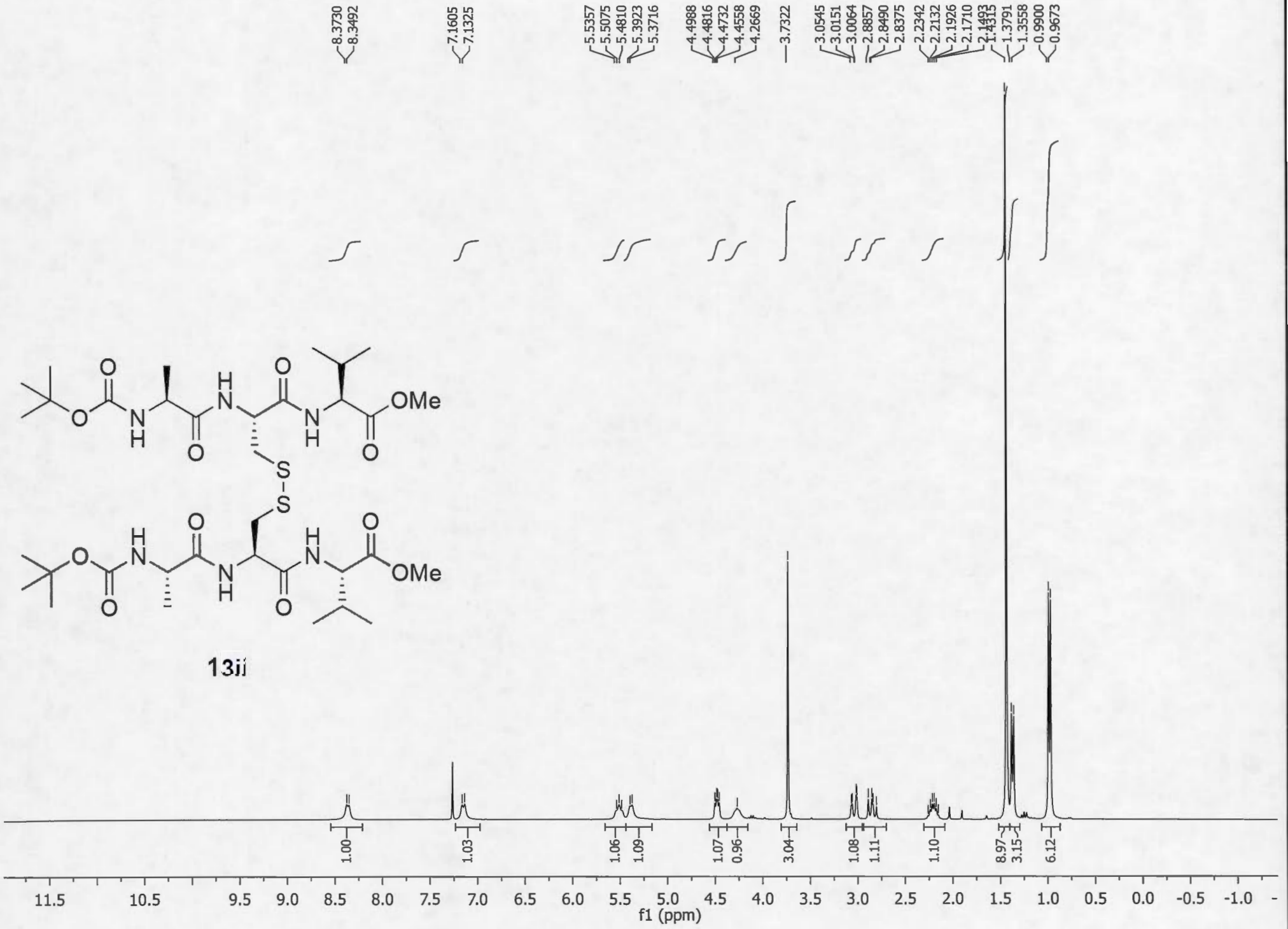
13i

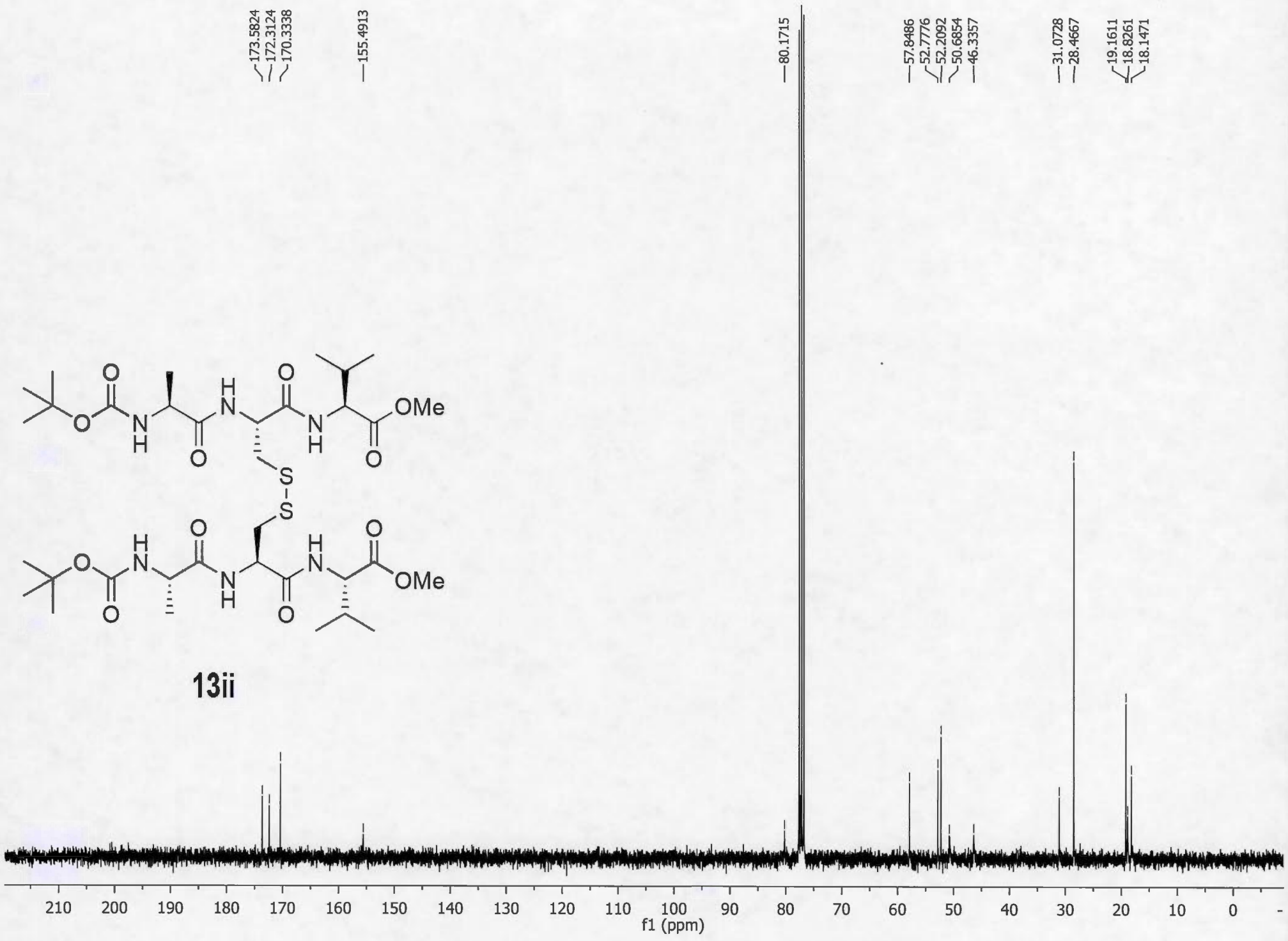
7.3911
7.3618
5.5728
5.5432
4.7009
4.6740
4.5069
4.4859
4.4769
4.4575
3.7099
3.6723
3.1035
3.0738
3.0545
3.0485
3.0181
2.9711
2.9355
2.2130
2.1907
2.1683
2.1460
2.1237
1.4522
0.9678
0.9564
0.9443
0.9338
0.90
1.05
0.99
1.07
3.00
2.07
1.03
9.07
6.05
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

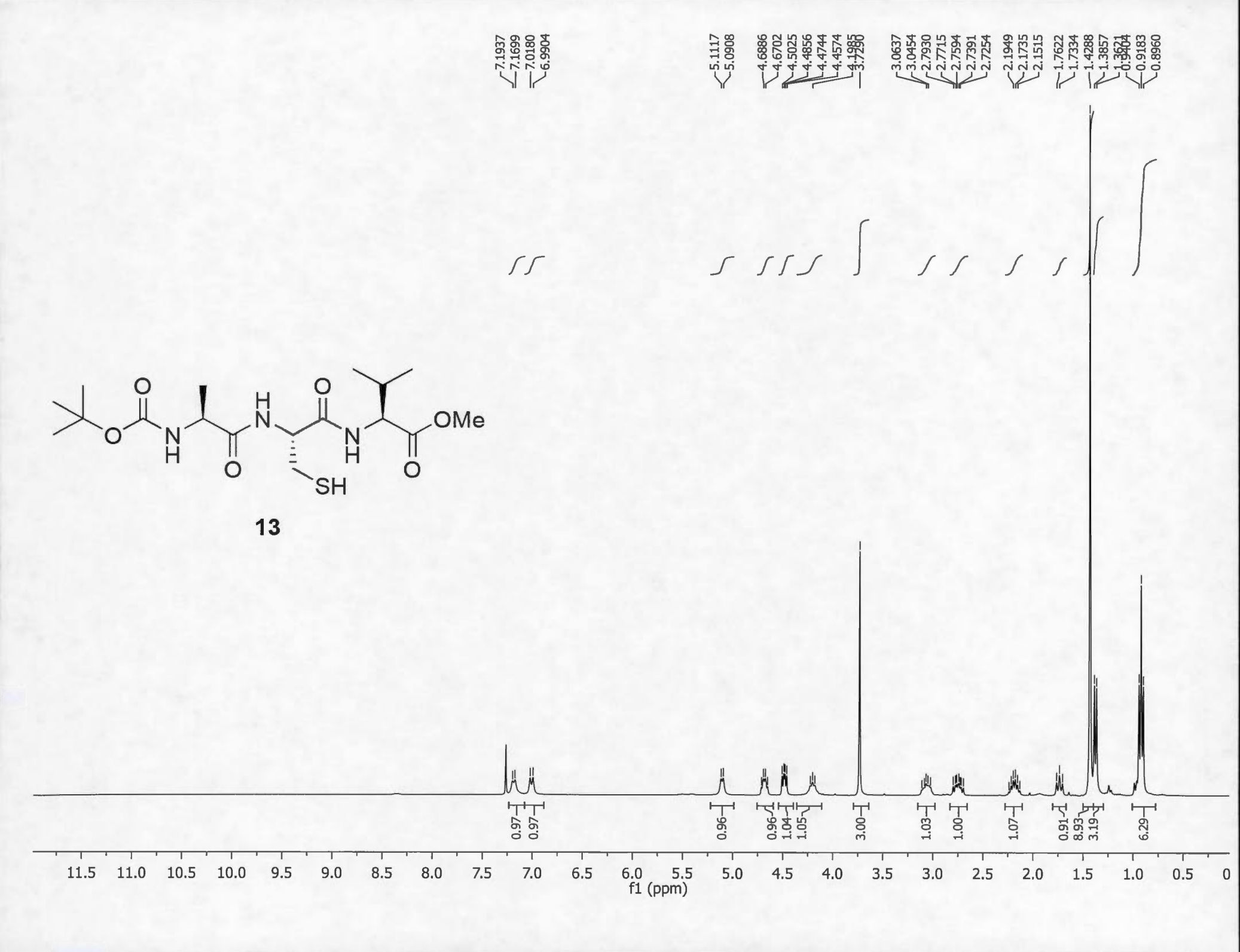


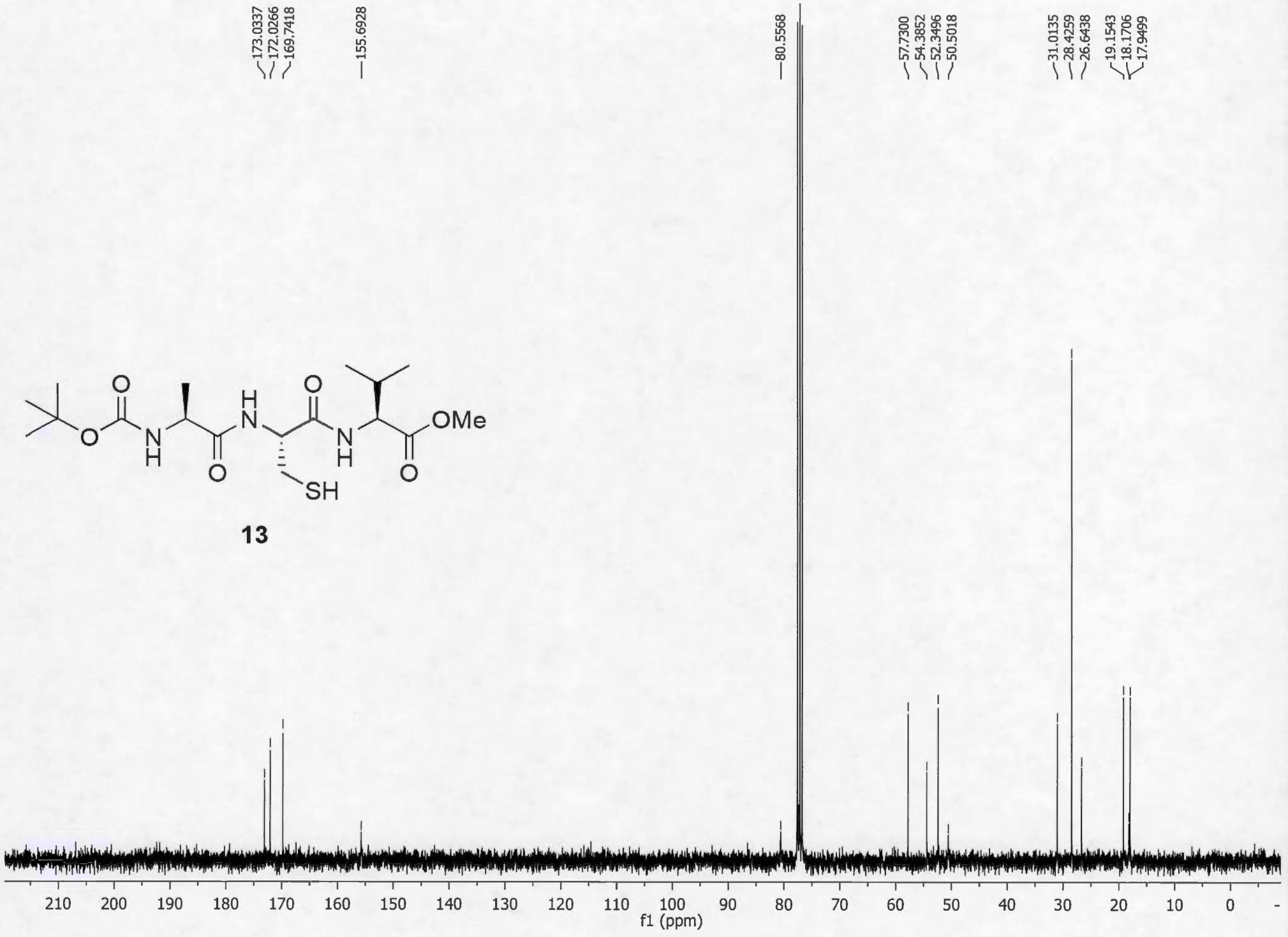
13i

172.0581
170.5409
155.7319
80.3658
57.9338
54.1737
52.2033
44.8505
30.9627
28.4383
19.2912
18.5264
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

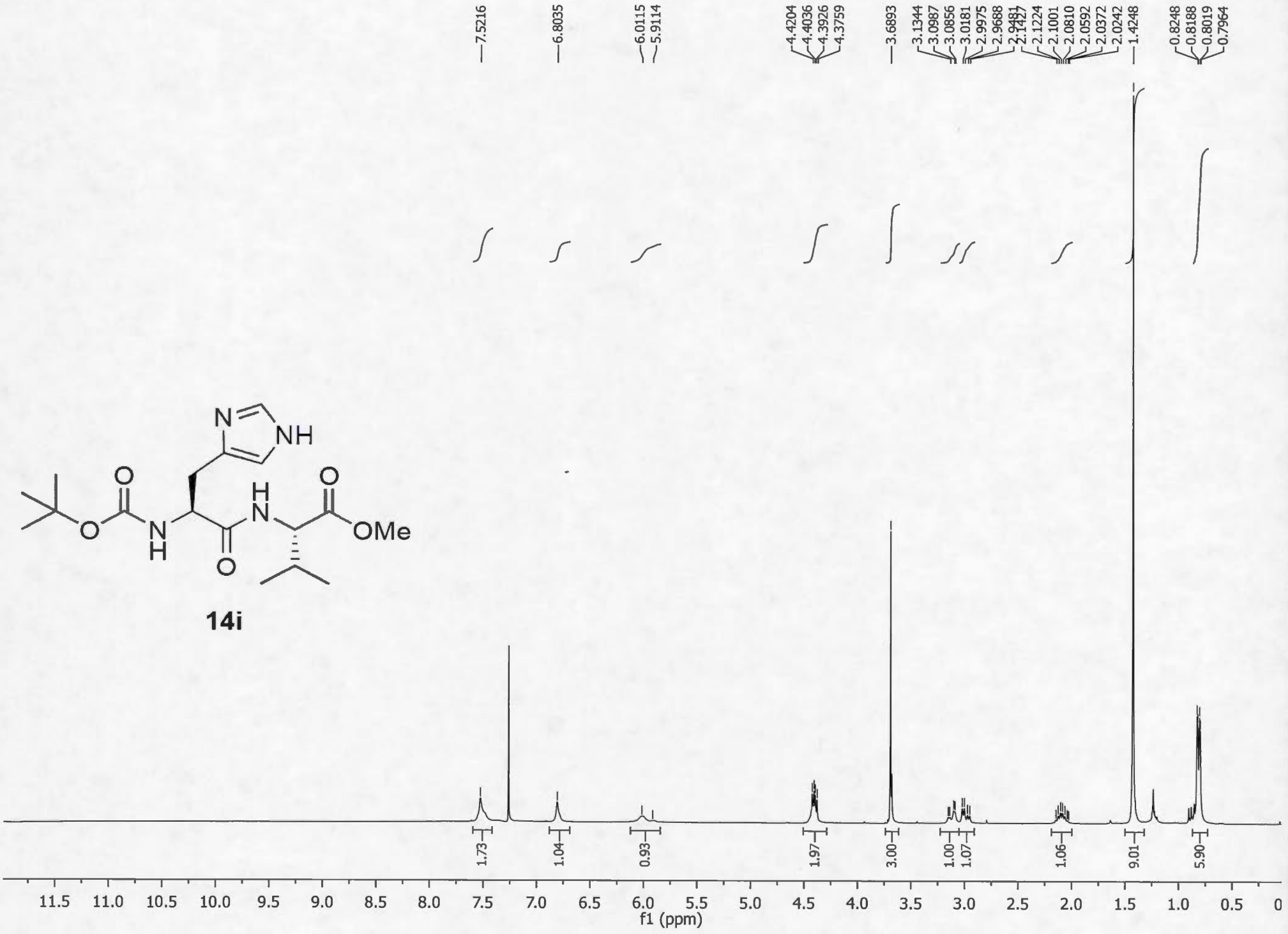

8.3730
8.3492
7.1605
7.1325
5.5357
5.5075
5.4810
5.3923
5.3716
4.4988
4.4816
4.4732
4.4558
4.2669
3.7322
3.0545
3.0151
3.0064
2.8857
2.8490
2.8375
2.2342
2.2132
2.1926
2.1710
2.1493
2.1315
1.3791
1.3558
0.9900
0.9673
OMe
OMe
13ii
1.00
1.03
1.06
1.09
1.07
0.96
3.04
1.08
1.11
1.10
8.97
3.15
6.12
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


173.5824
172.3124
170.3338
155.4913
80.1715
57.8486
52.7776
52.2092
50.6854
46.3357
31.0728
28.4667
19.1611
18.8261
18.1471
OMe
OMe
S
S
13ii
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

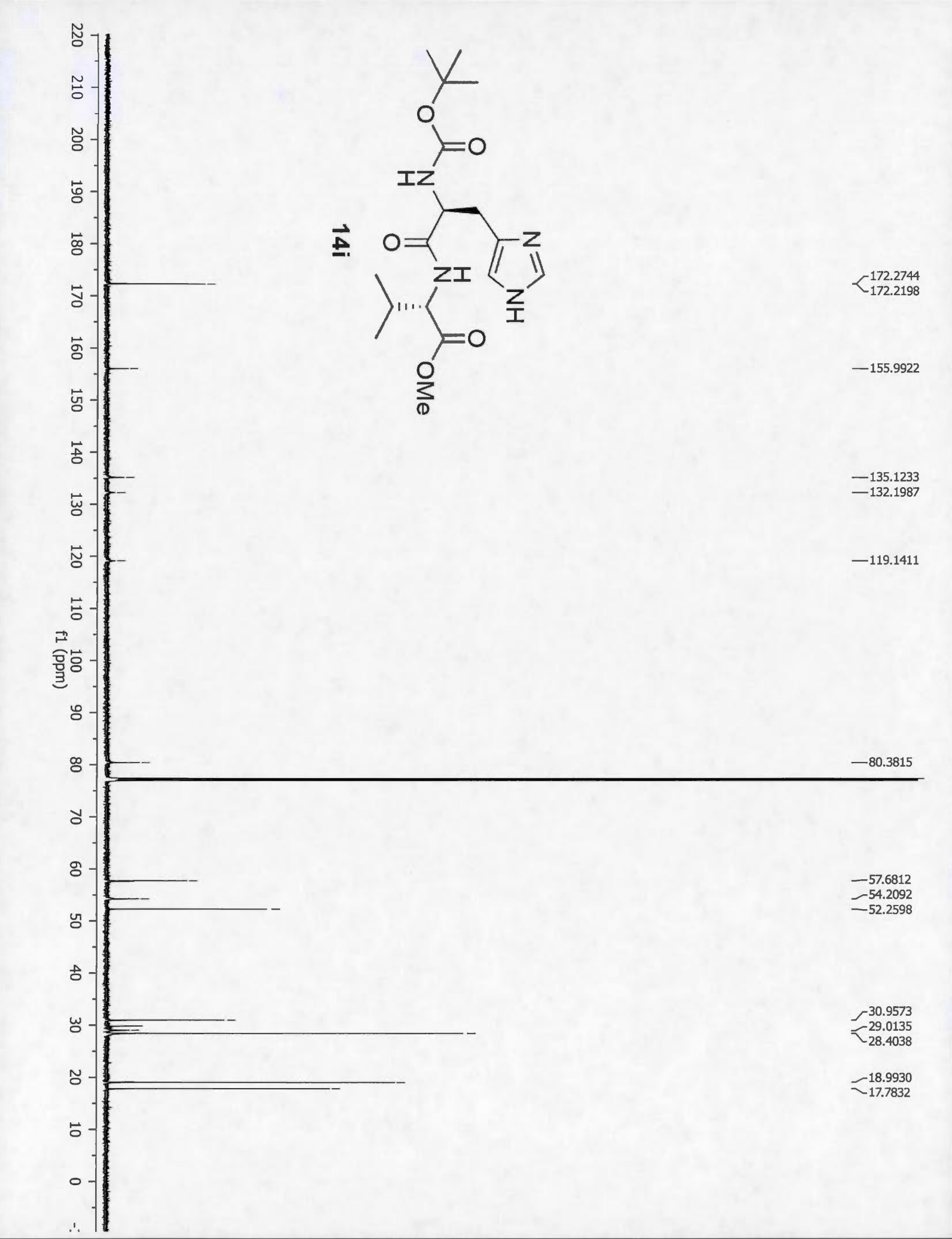

7.1937
7.1699
7.0180
6.9904
5.1117
5.0908
4.6886
4.6702
4.5025
4.4856
4.4744
4.4574
4.1985
3.7290
3.0637
3.0454
2.7930
2.7715
2.7594
2.7391
2.7254
2.1949
2.1735
2.1515
1.7622
1.7334
1.4288
1.3857
1.3621
0.9304
0.9183
0.8960
O
O
N
H
O
H
N
O
N
H
O
OMe
SH
13
0.97
0.97
0.96
0.96
1.04
1.05
3.00
1.03
1.00
1.07
0.91
8.93
3.19
6.29
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


173.0337
172.0266
169.7418
155.6928
80.5568
57.7300
54.3852
52.3496
50.5018
31.0135
28.4259
26.6438
19.1543
18.1706
17.9499
OMe
SH
f1 (ppm)

13


7.5216
6.8035
6.0115
5.9114
4.4204
4.4036
4.3926
4.3759
3.6893
3.1344
3.0987
3.0856
3.0181
2.9975
2.9688
2.9481
2.1427
2.1224
2.1001
2.0810
2.0592
2.0372
2.0242
1.4248
0.8248
0.8188
0.8019
0.7964
1.73
1.04
0.93
1.97
3.00
1.00
1.07
1.06
9.01
5.90
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)
N
NH
O
O
N
H
H
N
O
O
OMe

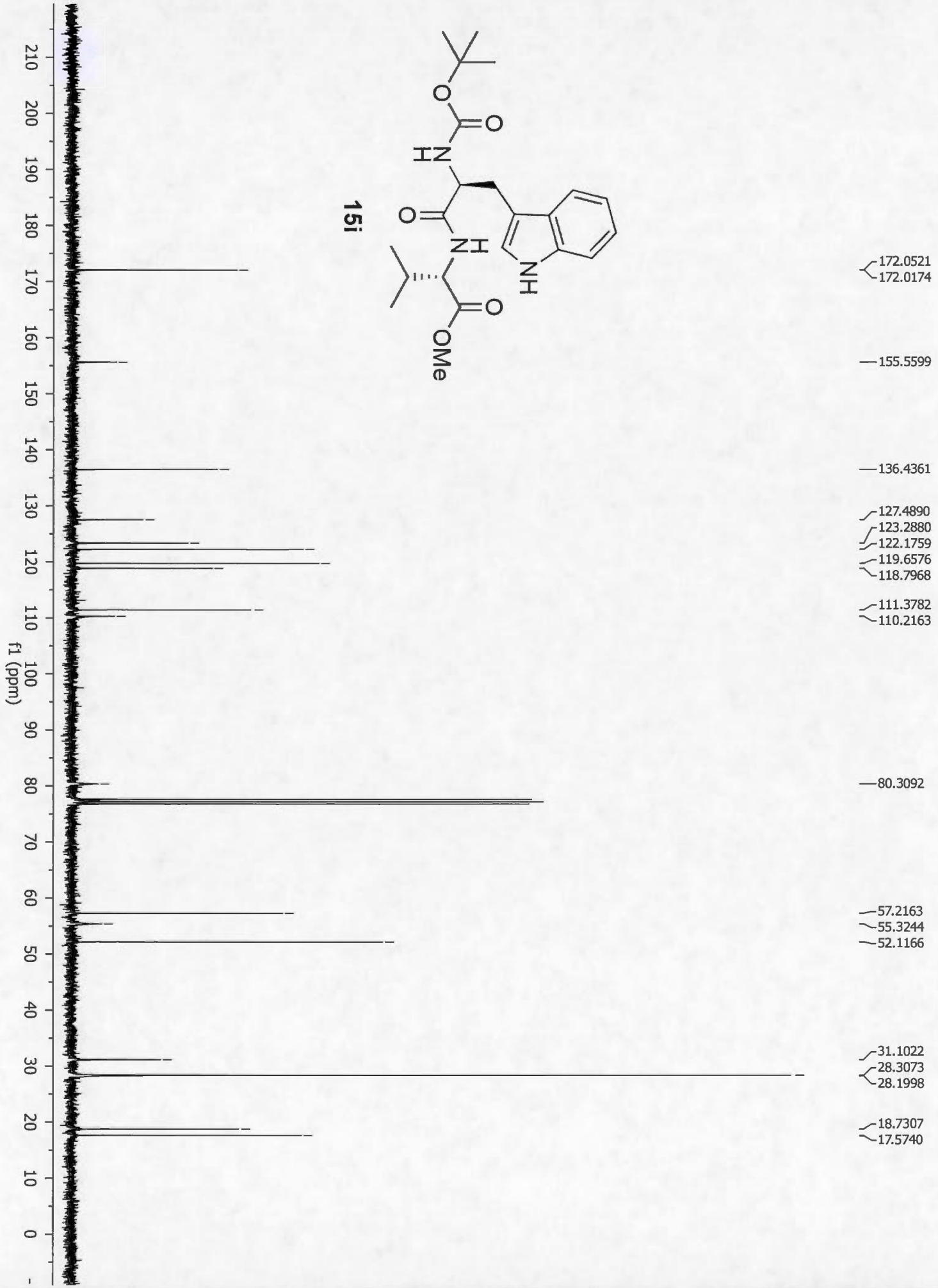
14i

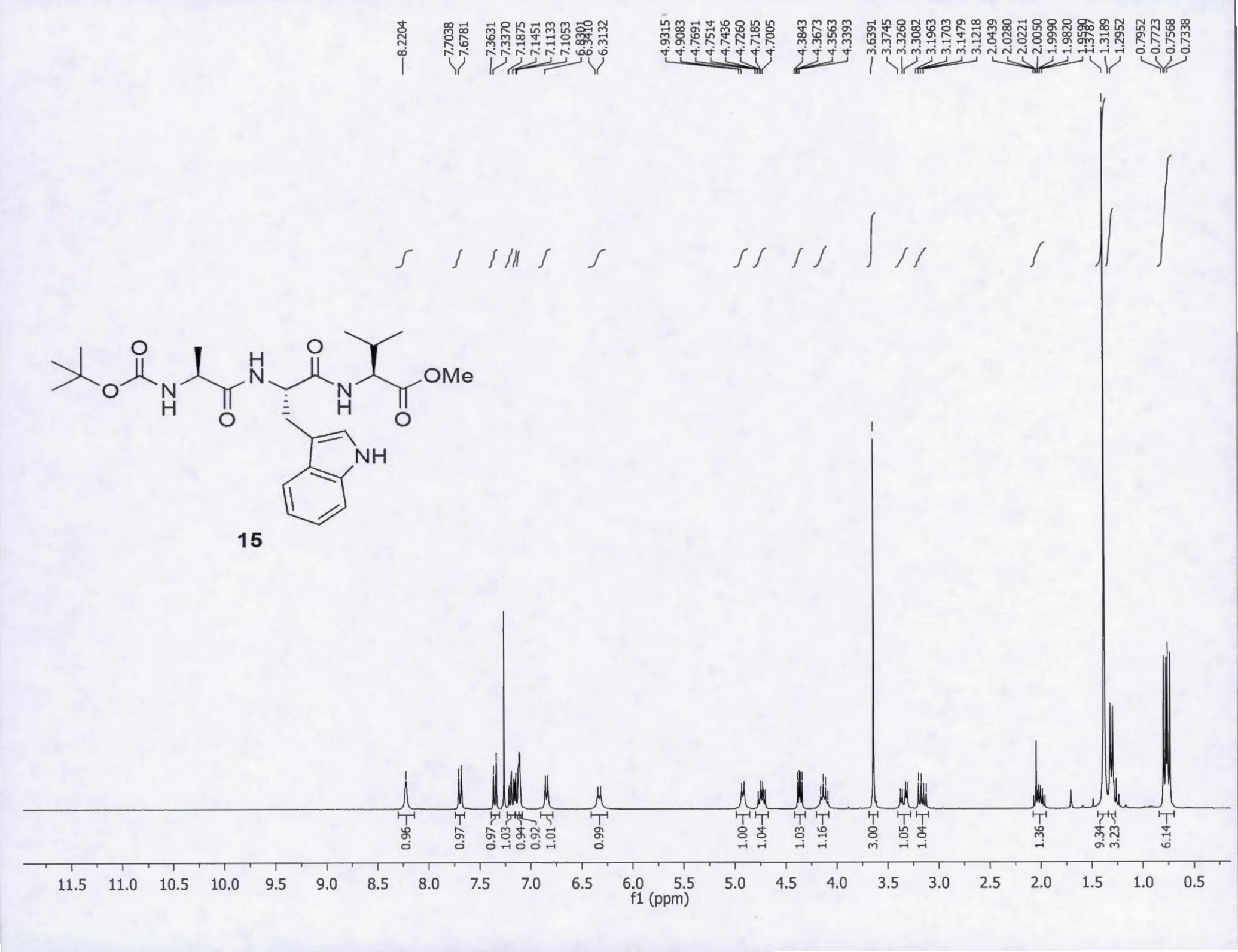

14i
172.2744
172.2198
155.9922
135.1233
132.1987
119.1411
80.3815
57.6812
54.2092
52.2598
30.9573
29.0135
28.4038
18.9930
17.7832
f1 (ppm)

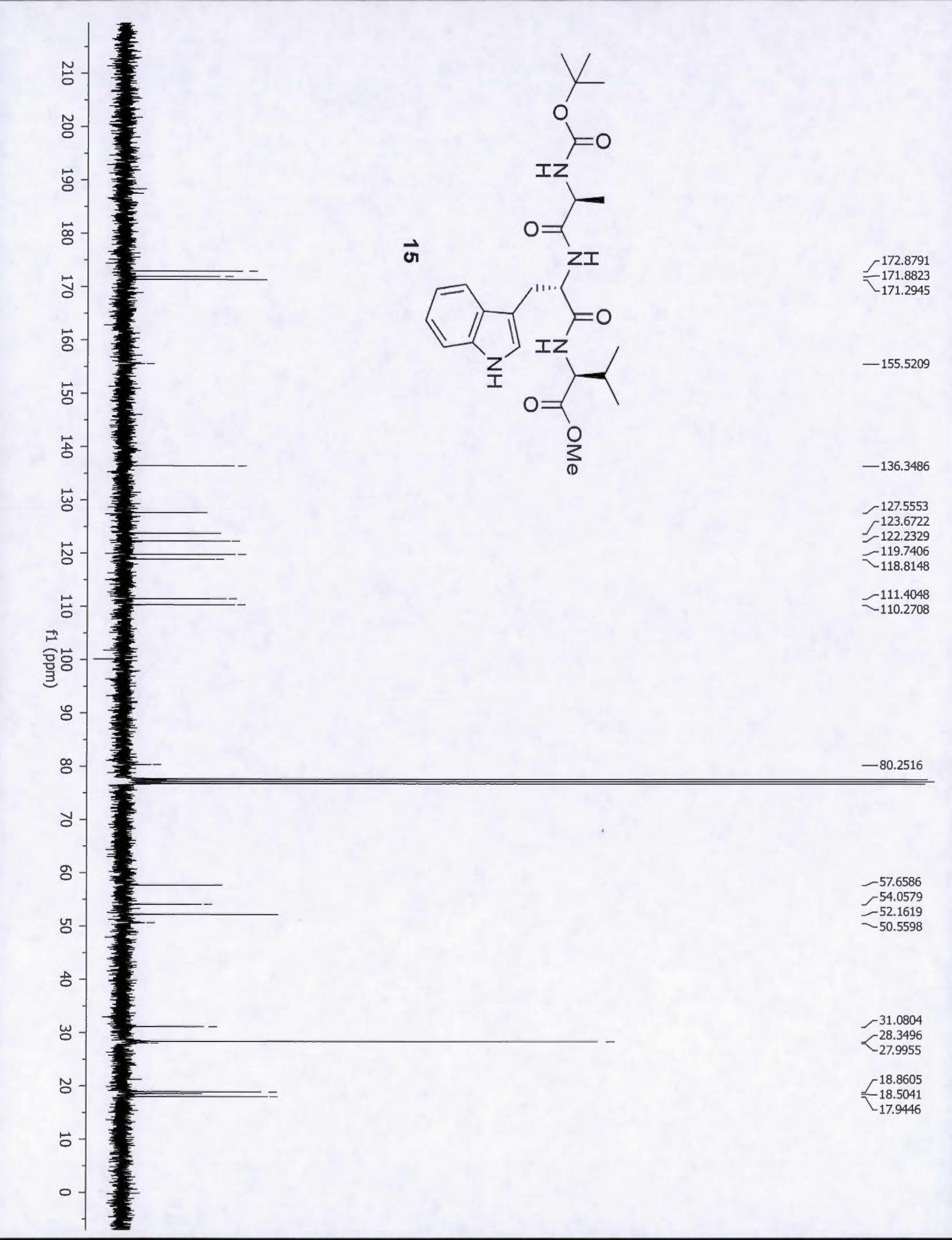
14
OMe
f1 (ppm)
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1.20
1.19
1.03
1.15
0.74
1.14
1.09
1.07
1.08
3.00
2.03
1.05
8.71
3.09
6.03
7.8825
7.6076
7.5805
7.5089
6.7800
5.3874
5.3693
5.2869
4.7616
4.7427
4.7198
4.4022
4.3848
4.3748
4.3574
4.1813
3.6992
3.1470
3.0968
3.0803
3.0543
3.0345
3.0045
2.9848
2.1399
2.1220
2.1166
2.0993
2.0942
2.0757
1.4140
1.3745
1.3511
0.8439
0.8283
0.8214
0.8051

14
O
O
HN
O
NH
N
NH
O
HN
O
OMe
173.4588
172.2438
171.2507
155.7548
134.8997
131.9359
118.9667
80.1190
57.8681
53.1961
52.2113
50.6214
30.7452
28.8031
28.4114
19.0121
18.5359
17.9355
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

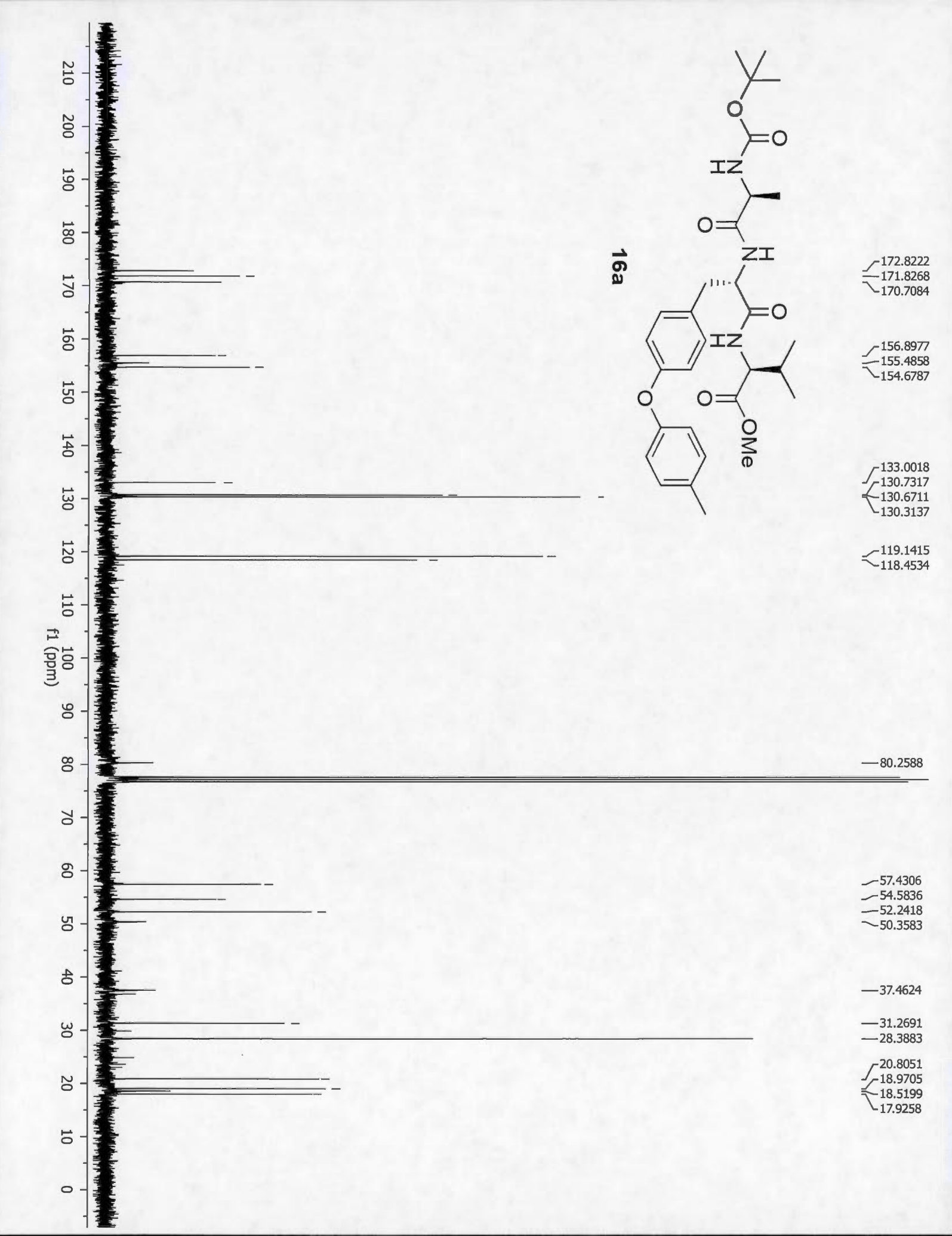
15i
OMe
f1 (ppm)
0.99
1.02
1.01
1.02
1.02
1.01
1.03
0.96
1.02
0.99
3.00
1.03
1.05
1.06
9.14
3.04
3.11
8.2042
7.6282
7.3665
7.3399
7.1932
7.1903
7.1670
7.1394
7.1365
7.1130
7.0669
7.0615
6.3647
6.3369
5.0896
4.5214
4.5008
4.4679
4.4518
4.4391
4.4231
3.6382
3.3544
3.3346
3.3054
3.2860
3.2374
3.2142
3.1886
3.1654
2.0398
2.0156
1.9930
1.9760
1.9535
1.9309
1.4149
0.7675
0.7450
0.7055
0.6826

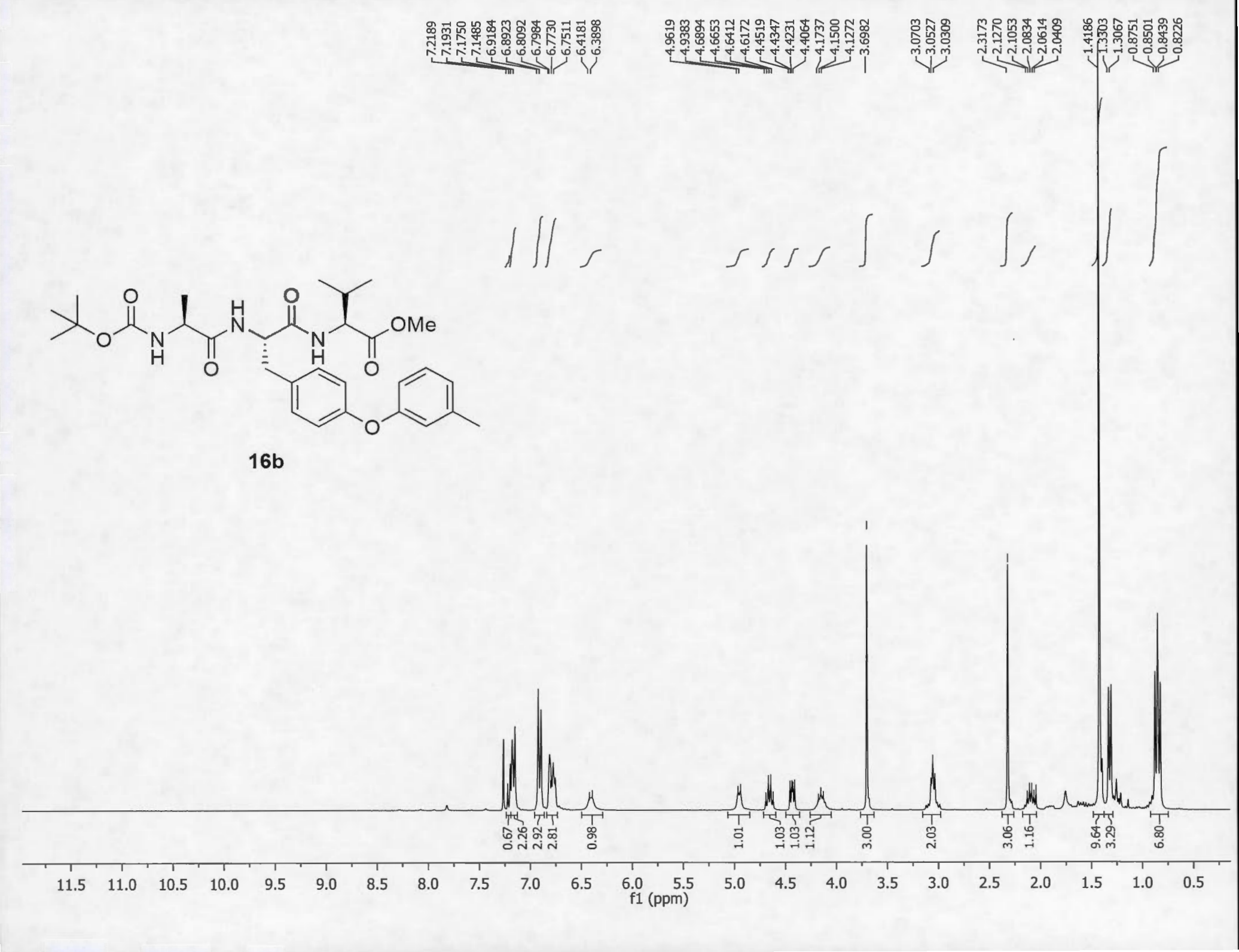

15i
172.0521
172.0174
155.5599
136.4361
127.4890
123.2880
122.1759
119.6576
118.7968
111.3782
110.2163
80.3092
57.2163
55.3244
52.1166
31.1022
28.3073
28.1998
18.7307
17.5740
f1 (ppm)

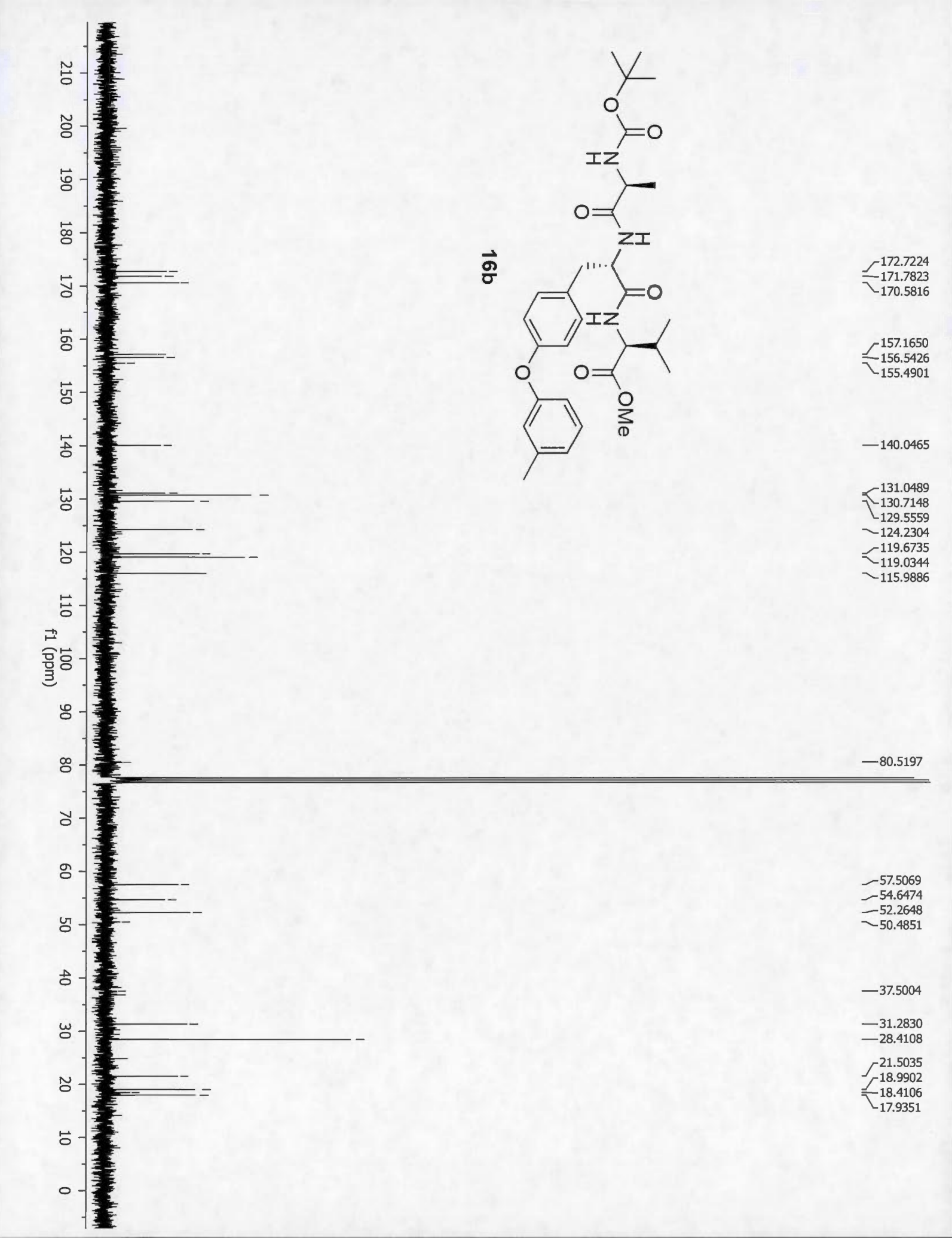

8.2204
7.7038
7.6781
7.3631
7.3370
7.1875
7.1451
7.1133
7.1053
6.8301
6.8210
6.3132
4.9315
4.9083
4.7691
4.7514
4.7436
4.7260
4.7185
4.7005
4.3843
4.3673
4.3563
4.3393
3.6391
3.3745
3.3260
3.3082
3.1963
3.1703
3.1479
3.1218
2.0439
2.0280
2.0221
2.0050
1.9990
1.9820
1.3189
1.2952
0.7952
0.7723
0.7568
0.7338
OMe
NH
15
0.96
0.97
0.97
1.03
0.94
0.92
1.01
0.99
1.00
1.04
1.03
1.16
3.00
1.05
1.04
1.36
9.34
3.23
6.14
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


15
172.8791
171.8823
171.2945
155.5209
136.3486
127.5553
123.6722
122.2329
119.7406
118.8148
111.4048
110.2708
80.2516
57.6586
54.0579
52.1619
50.5598
31.0804
28.3496
27.9955
18.8605
18.5041
17.9446
f1 (ppm)

16a
OMe
f1 (ppm)
3.69
4.62
0.99
0.98
1.01
1.02
1.02
3.00
2.00
2.95
1.08
9.20
3.05
6.31
7.1378
7.1183
7.1096
7.0916
6.8899
6.8798
6.8617
6.8513
6.6038
6.5807
5.1095
5.0854
4.7269
4.7031
4.6784
4.6548
4.4516
4.4343
4.4228
4.4057
3.6890
3.0367
3.0298
3.0143
3.0056
2.3143
2.1143
2.0972
2.0912
2.0741
2.0683
2.0511
1.4071
1.3158
1.2923
0.8662
0.8436
0.8362
0.8134


16a
172.8222
171.8268
170.7084
156.8977
155.4858
154.6787
133.0018
130.7317
130.6711
130.3137
119.1415
118.4534
80.2588
57.4306
54.5836
52.2418
50.3583
37.4624
31.2691
28.3883
20.8051
18.9705
18.5199
17.9258
f1 (ppm)


7.2189
7.1931
7.1750
7.1485
6.9184
6.8923
6.8092
6.7984
6.7730
6.7511
6.4181
6.3898
4.9619
4.9383
4.6894
4.6653
4.6412
4.6172
4.4519
4.4347
4.4231
4.4064
4.1737
4.1500
4.1272
3.6982
3.0703
3.0527
3.0309
2.3173
2.1270
2.1053
2.0834
2.0614
2.0409
1.4186
1.3303
1.3067
0.8751
0.8501
0.8439
0.8226
OMe
16b
0.67
2.26
2.92
2.81
0.98
1.01
1.03
1.03
1.12
3.00
2.03
3.06
1.16
9.64
3.29
6.80
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

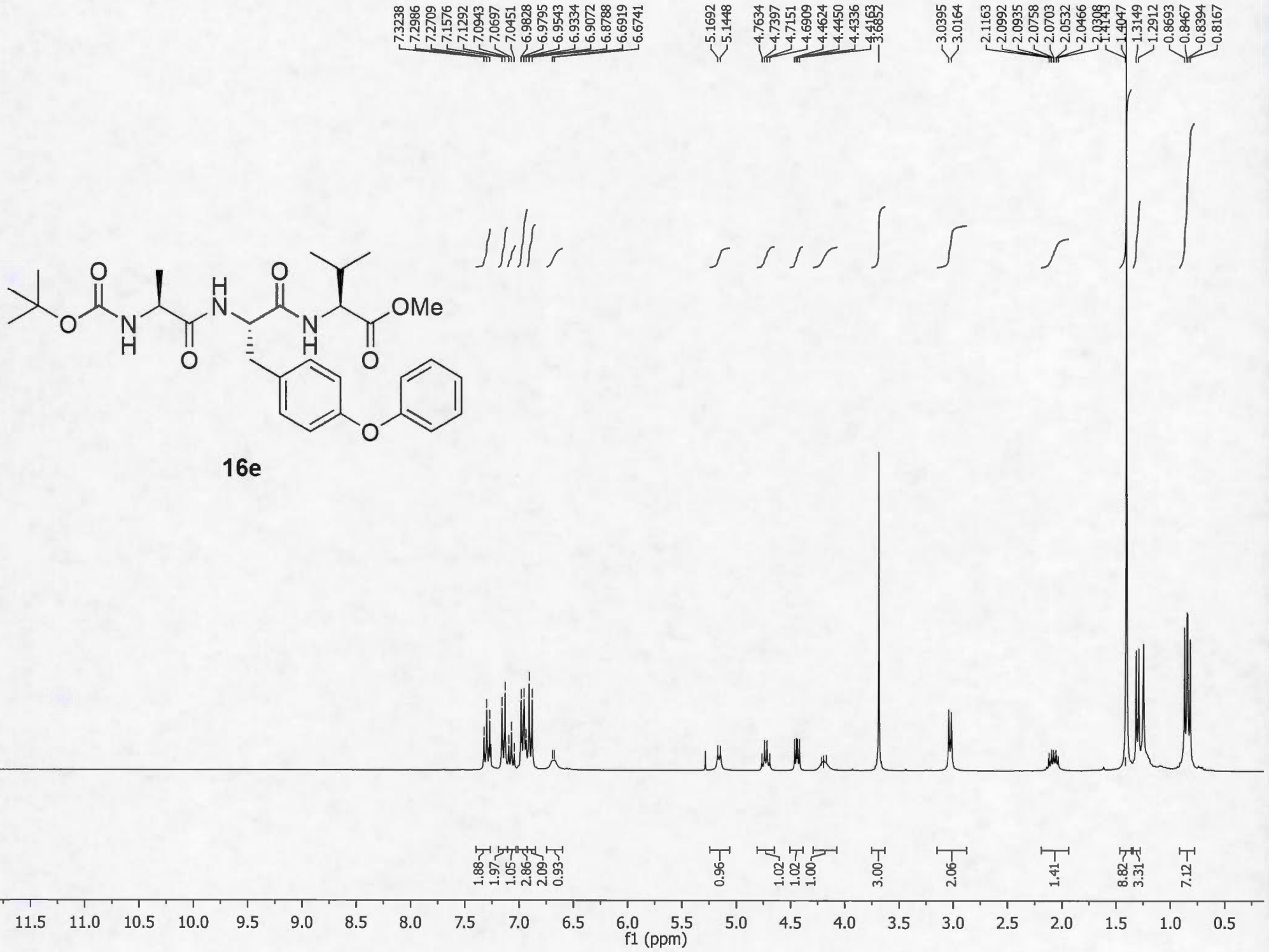

16b
172.7224
171.7823
170.5816
157.1650
156.5426
155.4901
140.0465
131.0489
130.7148
129.5559
124.2304
119.6735
119.0344
115.9886
80.5197
57.5069
54.6474
52.2648
50.4851
37.5004
31.2830
28.4108
21.5035
18.9902
18.4106
17.9351
f1 (ppm)

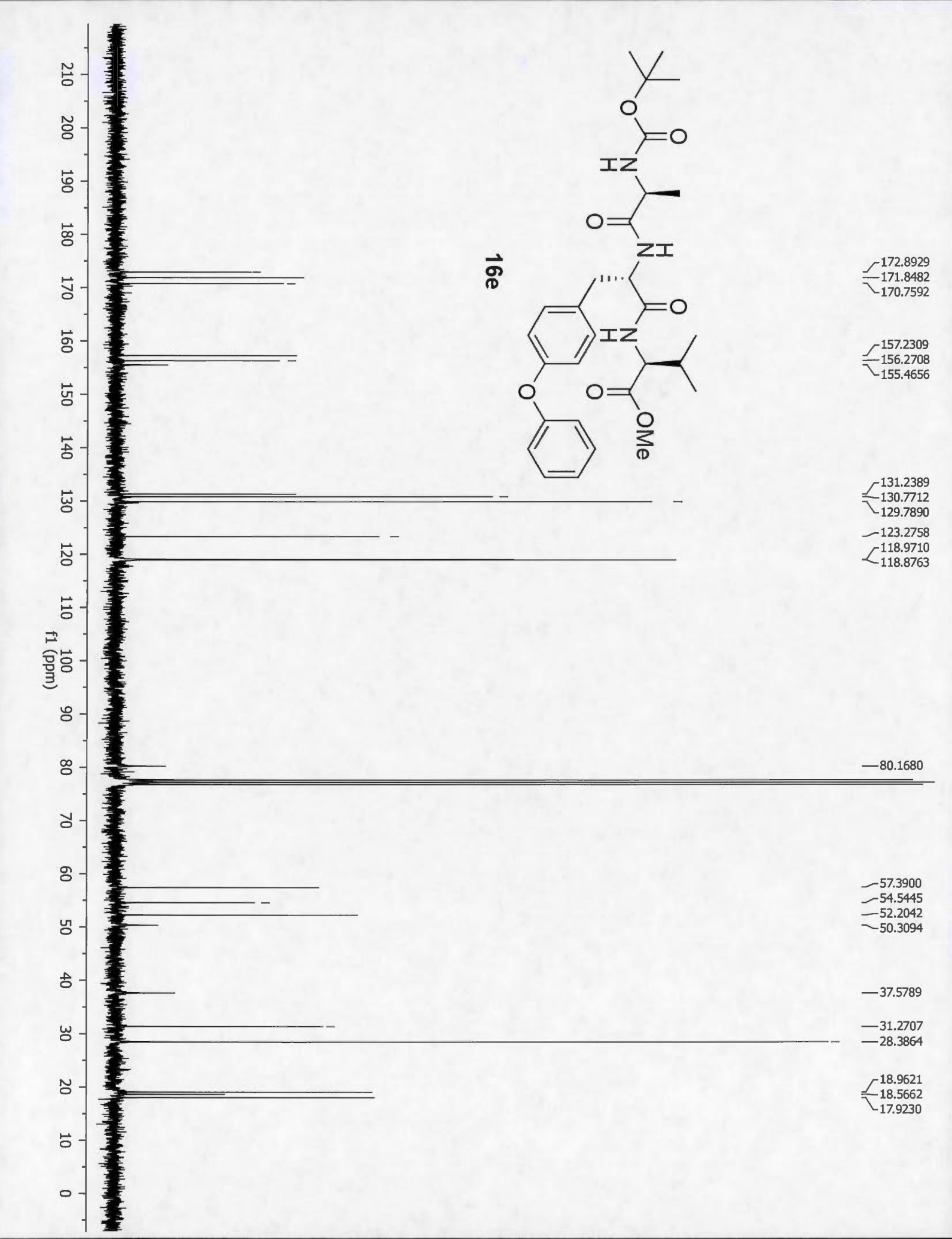
16c
OMe
f1 (ppm)
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
0.98
2.90
1.37
3.84
0.93
0.88
1.00
0.98
0.94
2.96
1.96
2.84
1.24
8.50
2.90
6.31
7.2371
7.2128
7.1614
7.1559
7.1367
7.1083
7.0666
7.0626
7.0420
7.0382
7.0176
7.0138
6.8793
6.8763
6.8488
6.8167
6.7881
6.5264
5.0564
5.0326
4.6875
4.6631
4.4531
4.4361
4.4244
4.4072
4.1621
3.6932
3.0406
3.0342
3.0188
3.0103
2.2080
2.1194
2.1021
2.0963
2.0792
2.0735
2.0563
1.4108
1.3181
1.2947
0.8670
0.8443
0.8368
0.8138

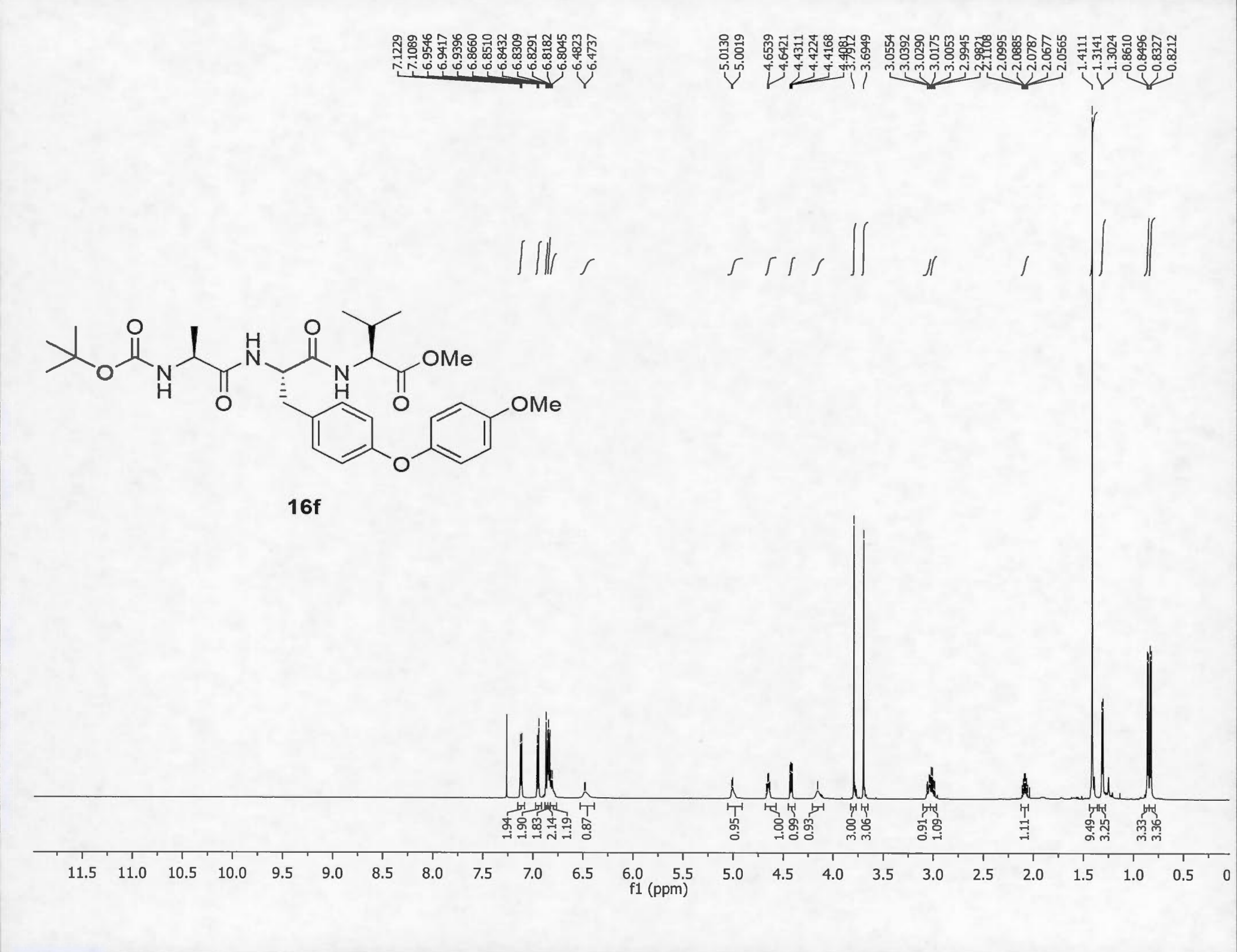
16c
OMe
172.8403
171.8337
170.7468
156.9625
155.4770
154.5551
131.5007
130.6873
130.3475
129.9042
127.1971
124.0240
119.6379
117.5695
80.2806
57.4573
54.5852
53.5352
52.1897
50.4369
37.4134
31.2353
28.3916
18.9590
18.5060
17.9229
16.2328
f1 (ppm)

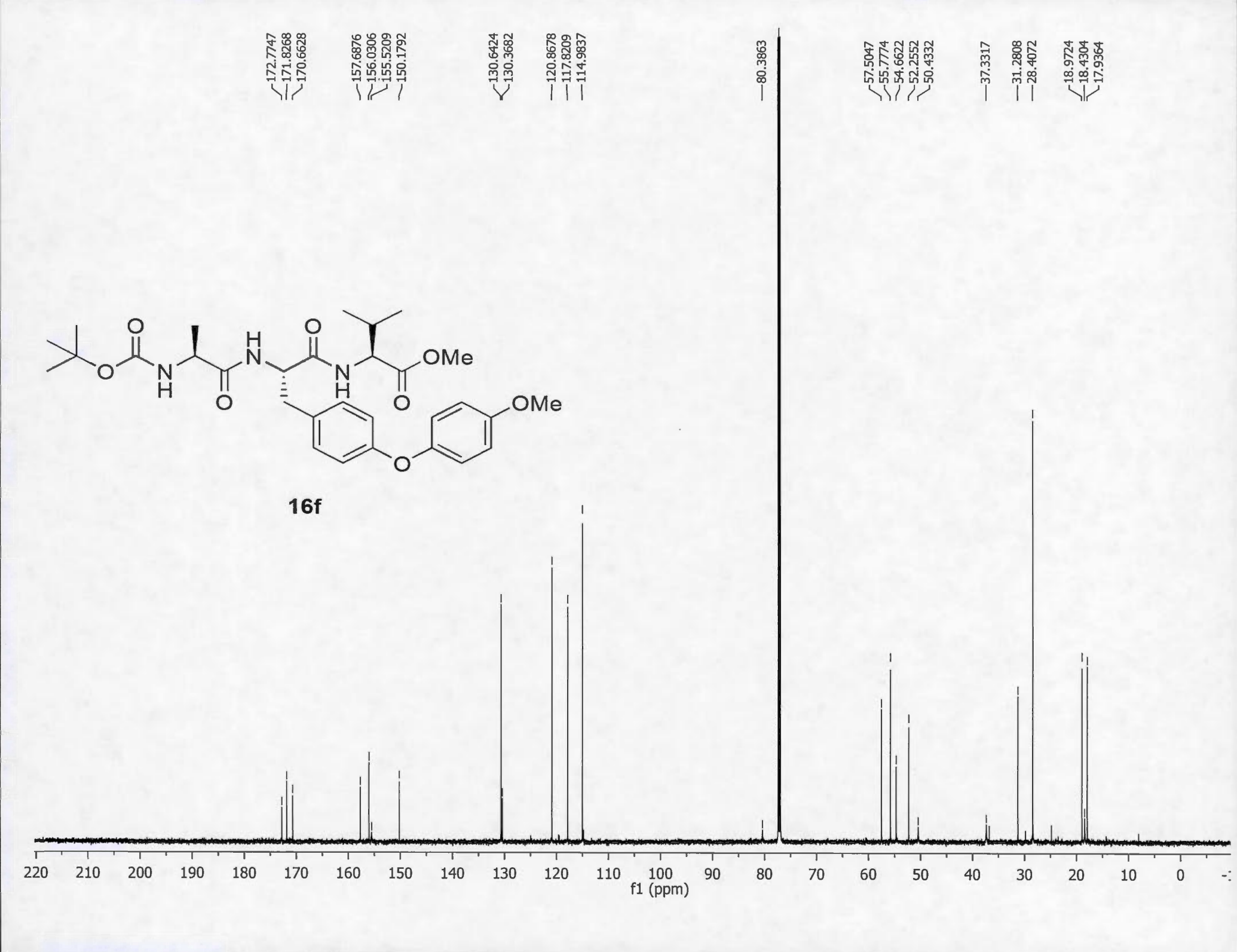
16d
OMe
f1 (ppm)
2.07
2.12
0.50
1.10
1.84
1.15
1.09
1.12
1.07
1.16
3.00
2.04
6.16
1.48
9.08
3.13
6.55
7.1124
7.0996
7.0839
7.0686
7.0583
7.0436
6.9539
6.9305
6.7301
6.7047
6.6898
6.6801
6.6514
6.3783
6.3576
4.9057
4.8888
4.6496
4.6263
4.6013
4.5782
4.4406
4.4238
4.4122
4.3953
4.1299
4.1066
3.6962
3.0266
3.0038
2.0979
2.0416
2.0321
2.0253
2.0132
1.9893
1.9790
1.4183
1.3061
1.2824
0.8580
0.8352
0.8226
0.7995

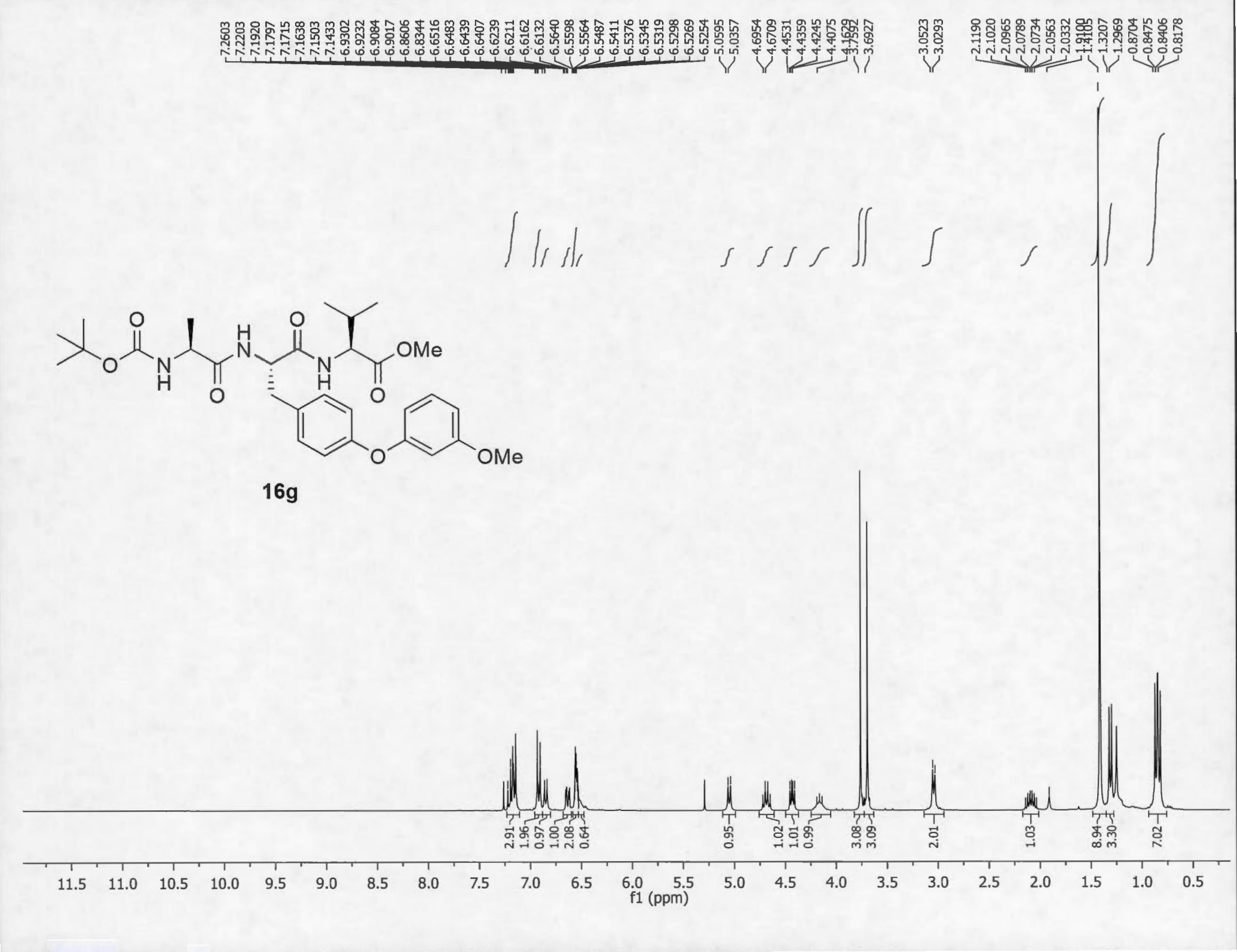
16d
172.7087
171.8339
170.6666
157.0750
155.5856
151.1875
131.5406
130.6874
129.1721
129.1163
125.2133
114.9486
80.4720
57.5006
54.6350
52.2300
50.4648
37.1799
31.1778
28.4189
18.9872
18.4229
17.8990
16.4564
f1 (ppm)


7.3238
7.2986
7.2709
7.1576
7.1292
7.0943
7.0697
7.0451
6.9828
6.9795
6.9543
6.9334
6.9072
6.8788
6.6919
6.6741
5.1692
5.1448
4.7634
4.7397
4.7151
4.6909
4.4624
4.4450
4.4336
4.4163
3.6852
3.0395
3.0164
2.1163
2.0992
2.0935
2.0758
2.0703
2.0532
2.0466
1.4047
1.3149
1.2912
0.8693
0.8467
0.8394
0.8167
OMe
16e
1.88
1.97
1.05
2.86
2.09
0.93
0.96
1.02
1.02
1.00
3.00
2.06
1.41
8.82
3.31
7.12
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


16e
172.8929
171.8482
170.7592
157.2309
156.2708
155.4656
131.2389
130.7712
129.7890
123.2758
118.9710
118.8763
80.1680
57.3900
54.5445
52.2042
50.3094
37.5789
31.2707
28.3864
18.9621
18.5662
17.9230
f1 (ppm)


7.1229
7.1089
6.9546
6.9417
6.9396
6.8660
6.8510
6.8432
6.8309
6.8291
6.8182
6.8045
6.4823
6.4737
5.0130
5.0019
4.6539
4.6421
4.4311
4.4224
4.4168
4.4081
3.7912
3.6949
3.0554
3.0392
3.0290
3.0175
3.0053
2.9945
2.9821
2.1108
2.0995
2.0885
2.0787
2.0677
2.0565
1.4111
1.3141
1.3024
0.8610
0.8496
0.8327
0.8212
OMe
OMe
16f
1.94
1.90
1.83
2.14
1.19
0.87
0.95
1.00
0.99
0.93
3.00
3.06
0.91
1.09
1.11
9.49
3.25
3.33
3.36
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


172.7747
171.8268
170.6628
157.6876
156.0306
155.5209
150.1792
130.6424
130.3682
120.8678
117.8209
114.9837
80.3863
57.5047
55.7774
54.6622
52.2552
50.4332
37.3317
31.2808
28.4072
18.9724
18.4304
17.9364
OMe
OMe
16f
f1 (ppm)


7.2603
7.2203
7.1920
7.1797
7.1715
7.1638
7.1503
7.1433
6.9302
6.9232
6.9084
6.9017
6.8606
6.8344
6.6516
6.6483
6.6439
6.6407
6.6239
6.6211
6.6162
6.6132
6.5640
6.5598
6.5564
6.5487
6.5411
6.5376
6.5345
6.5319
6.5298
6.5269
6.5254
5.0595
5.0357
4.6954
4.6709
4.4531
4.4359
4.4245
4.4075
4.1629
4.1592
3.7592
3.6927
3.0523
3.0293
2.1190
2.1020
2.0965
2.0789
2.0734
2.0563
2.0332
1.9100
1.4105
1.3207
1.2969
0.8704
0.8475
0.8406
0.8178
OMe
OMe
16g
2.91
1.96
0.97
1.00
2.08
0.64
0.95
1.02
1.01
0.99
3.08
3.09
2.01
1.03
8.94
3.30
7.02
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


16g
172.7847
171.8175
170.6240
161.0531
158.4758
156.1368
155.5112
131.3746
130.7569
130.2221
119.2260
110.9958
108.9498
105.0159
80.3985
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18.9841
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17.9304
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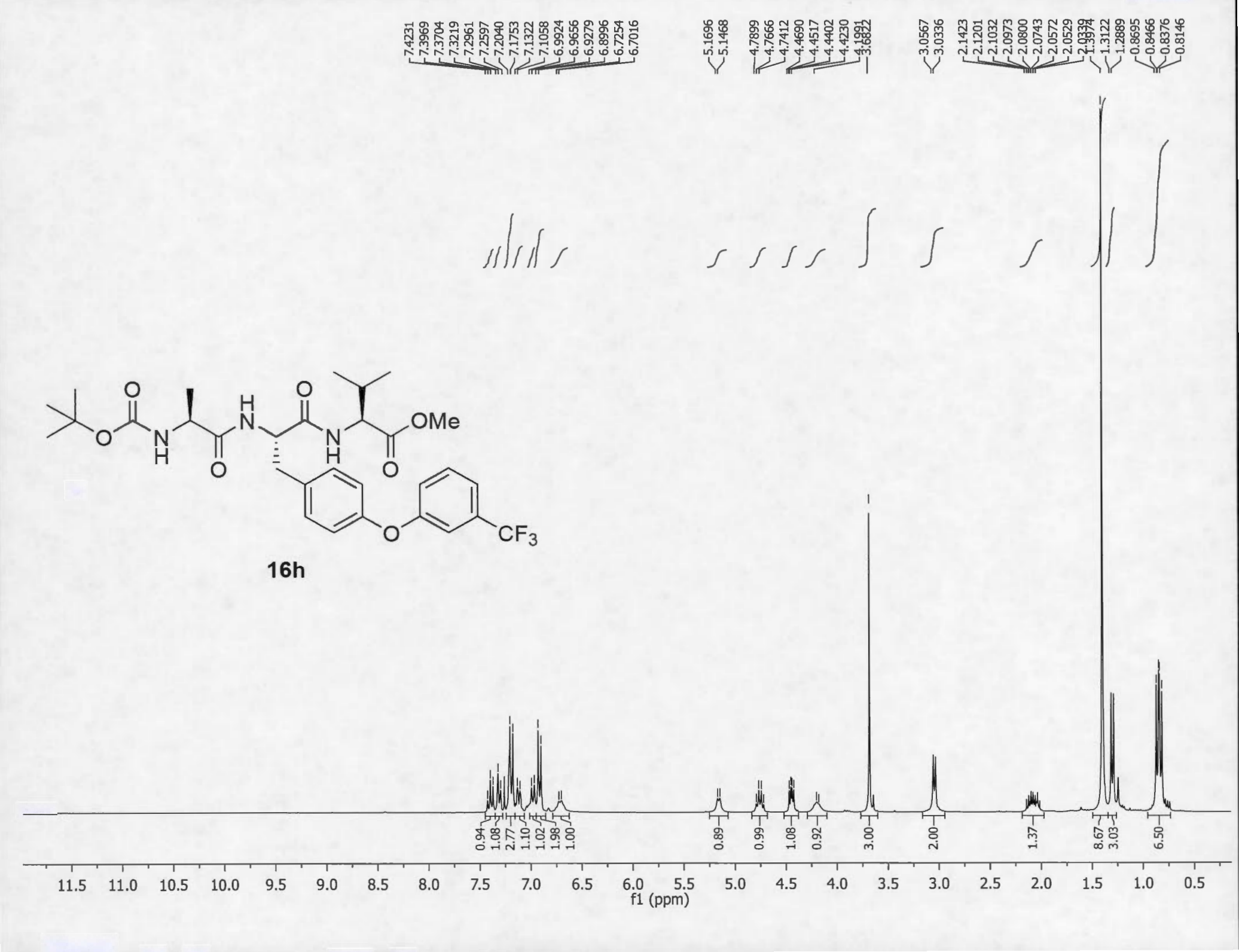
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6.9656
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6.8996
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6.7016
5.1696
5.1468
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4.7412
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3.0336
2.1423
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2.1032
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2.0800
2.0743
2.0572
2.0529
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0.8466
0.8376
0.8146
OMe
CF3
16h
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1.08
2.77
1.10
1.02
1.98
1.00
0.89
0.99
1.08
0.92
3.00
2.00
1.37
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3.03
6.50
11.5
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10.0
9.5
9.0
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6.5
6.0
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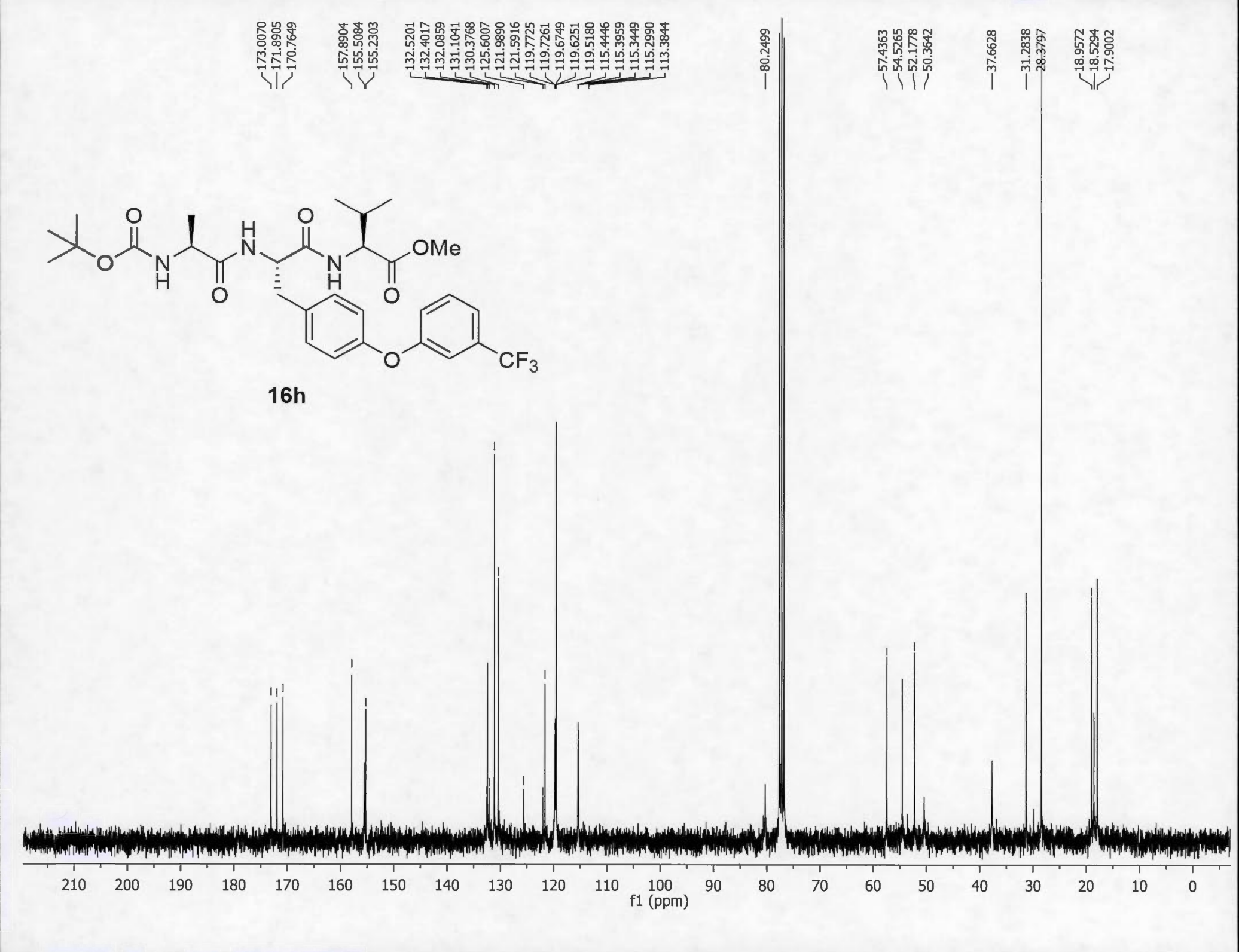
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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121.9890
121.5916
119.7725
119.7261
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119.6251
119.5180
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115.3959
115.3449
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113.3844
80.2499
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54.5265
52.1778
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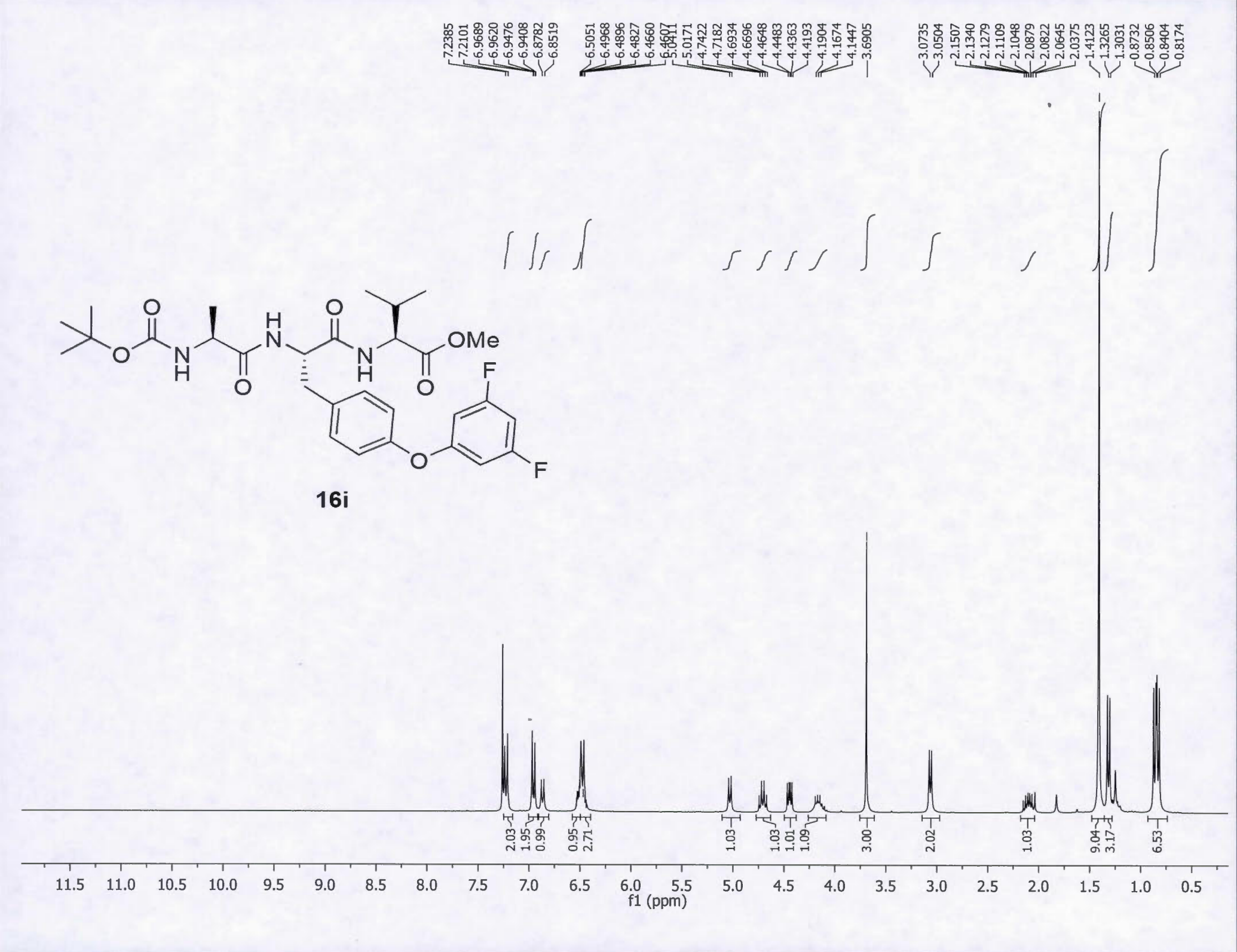
17.9002
OMe
CF3
16h
f1 (ppm)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6.4896
6.4827
6.4660
5.0171
4.7422
4.7182
4.6934
4.6696
4.6648
4.4483
4.4363
4.4193
4.1904
4.1674
4.1447
3.6905
3.0735
3.0504
2.1507
2.1340
2.1279
2.1109
2.1048
2.0879
2.0822
2.0645
2.0375
1.4123
1.3265
1.3031
0.8732
0.8506
0.8404
0.8174
O
O
N
H
O
N
H
O
OMe
O
F
O
F
16i
2.03
1.95
0.99
0.95
2.71
1.03
1.03
1.01
1.09
3.00
2.02
1.03
9.04
3.17
6.53
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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3.0
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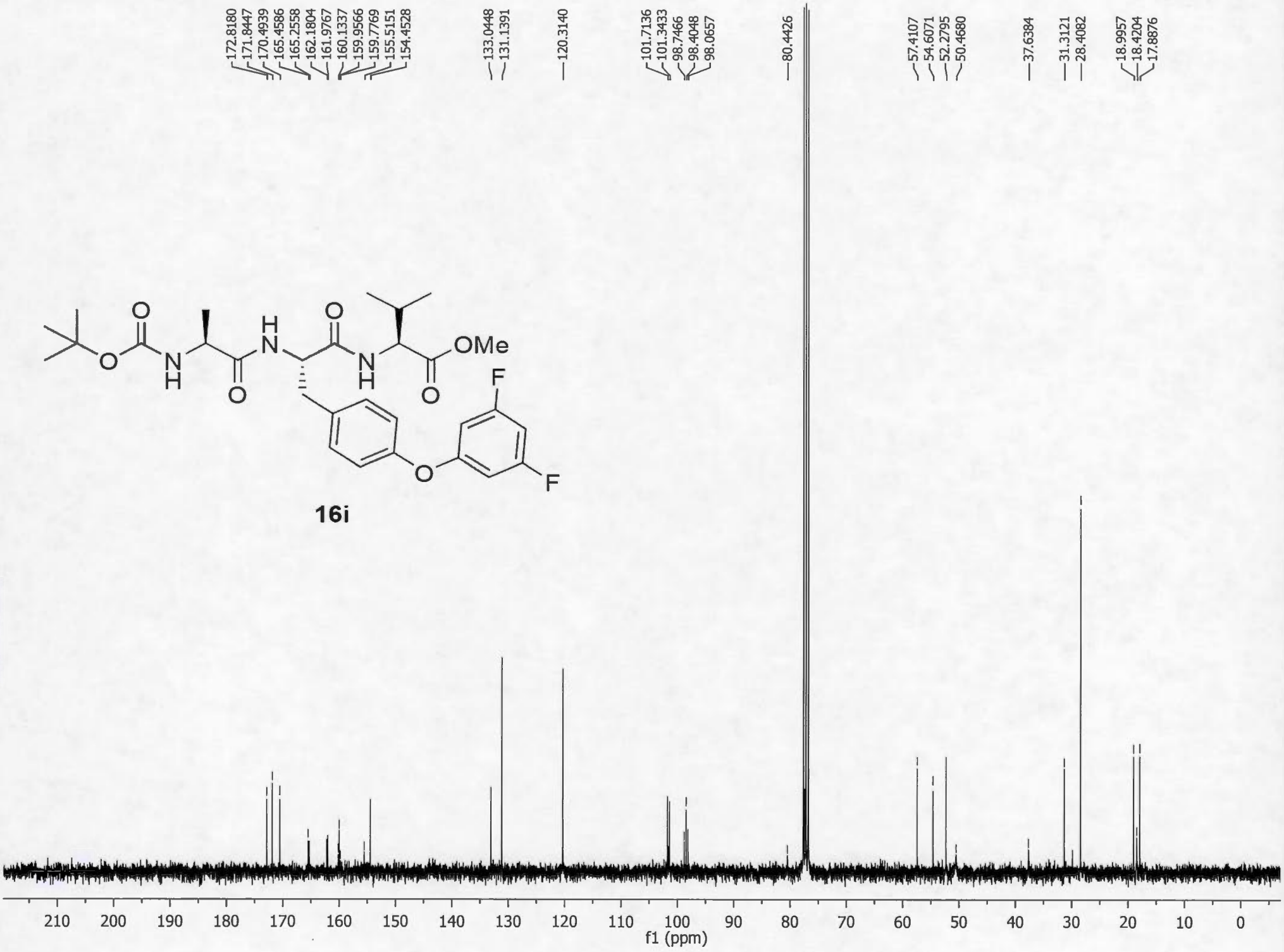
0.5
f1 (ppm)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159.9566
159.7769
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154.4528
133.0448
131.1391
120.3140
101.7136
101.3433
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98.4048
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80.4426
57.4107
54.6071
52.2795
50.4680
37.6384
31.3121
28.4082
18.9957
18.4204
17.8876
O
O
N
H
O
N
H
O
OMe
O
F
O
F
16i
210
200
190
180
170
160
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140
130
120
110
100
90
80
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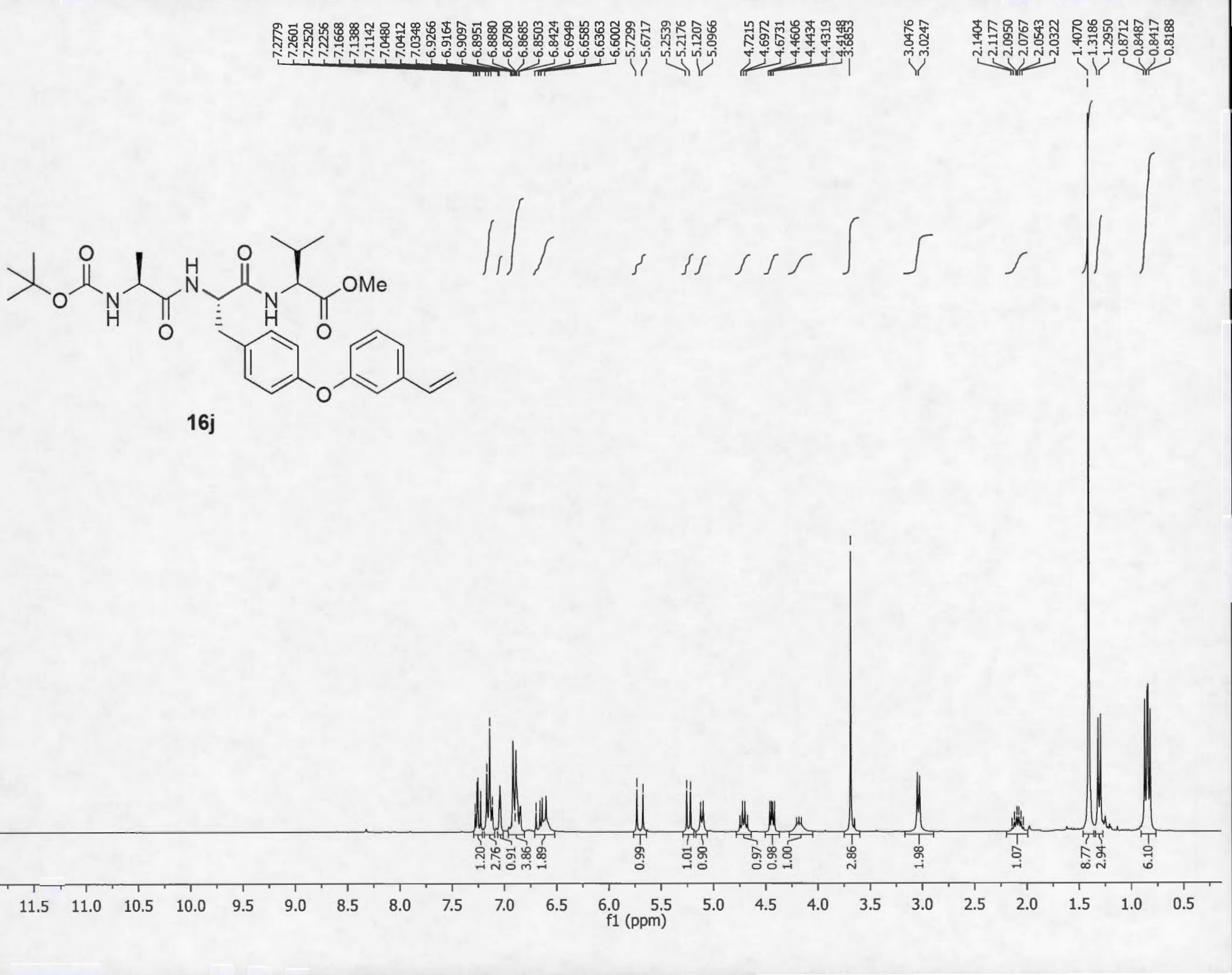
50
40
30
20
10
0
f1 (ppm)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7.2520
7.2256
7.1668
7.1388
7.1142
7.0480
7.0412
7.0348
6.9266
6.9164
6.9097
6.8951
6.8880
6.8780
6.8685
6.8503
6.8424
6.6949
6.6585
6.6363
6.6002
5.7299
5.6717
5.2539
5.2176
5.1207
5.0966
4.7215
4.6972
4.6731
4.4606
4.4434
4.4319
4.4148
3.6853
3.0476
3.0247
2.1404
2.1177
2.0950
2.0767
2.0543
2.0322
1.4070
1.3186
1.2950
0.8712
0.8487
0.8417
0.8188
OMe
16j
1.20
2.76
0.91
3.86
1.89
0.99
1.01
0.90
0.97
0.98
1.00
2.86
1.98
1.07
8.77
2.94
6.10
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

16j
172.8410
171.8342
170.6845
157.4741
156.3159
155.4913
139.6020
136.3511
131.2745
130.7967
129.8721
121.4401
118.9720
118.3242
116.6113
114.7506
80.3022
57.4429
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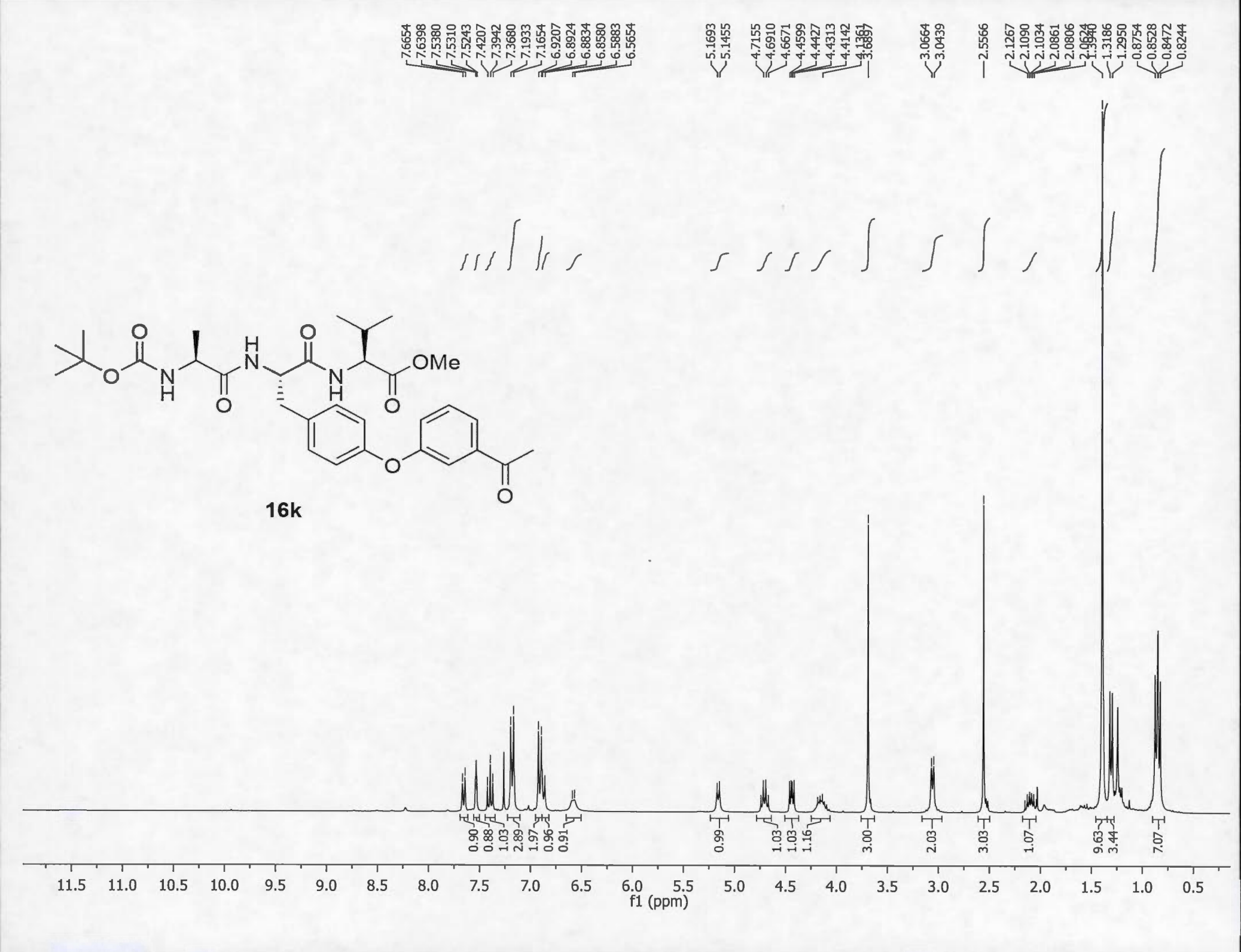
50.3860
37.5548
31.2930
28.4036
18.9795
18.5131
17.9343
f1 (ppm)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7.5243
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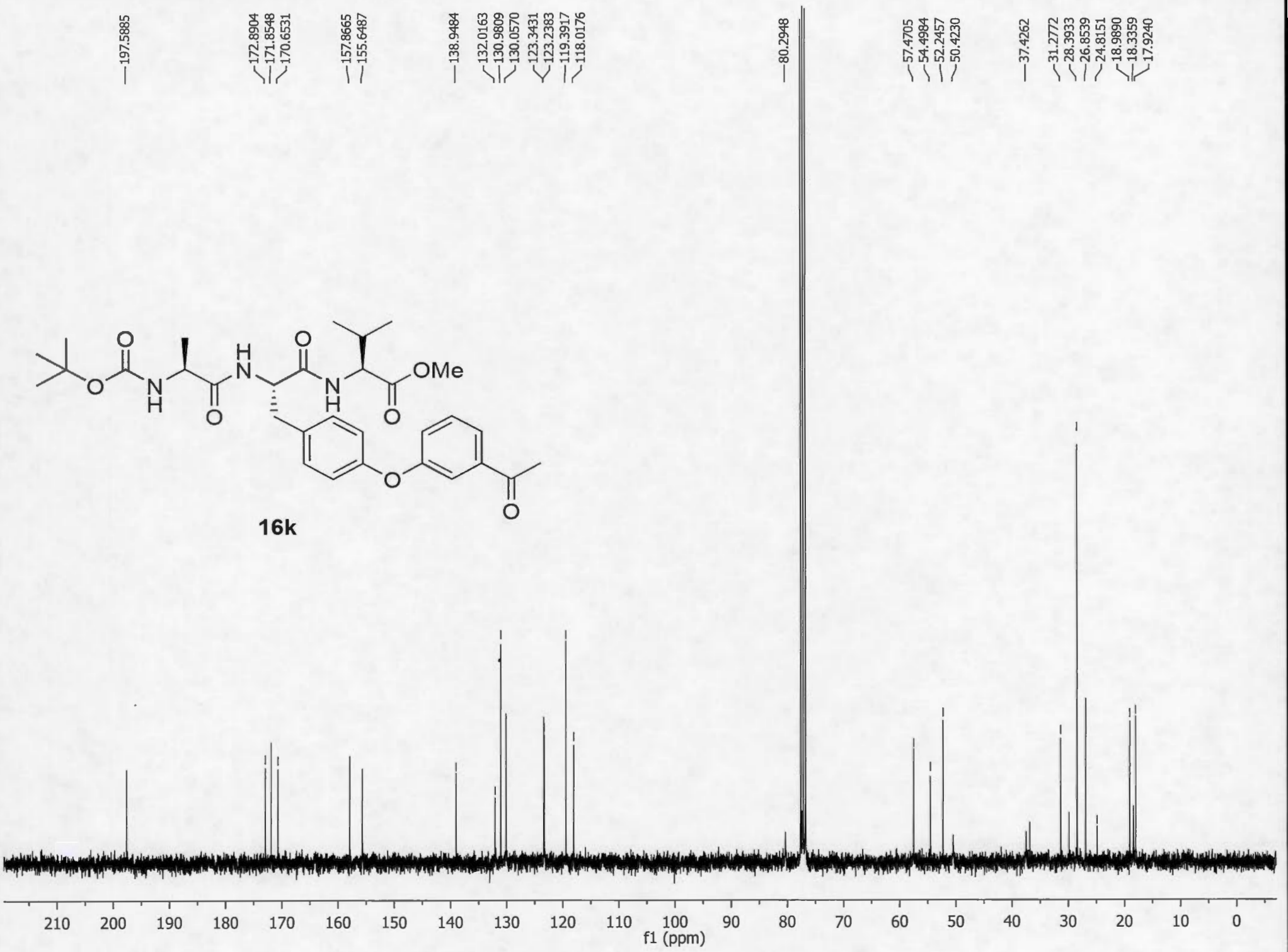
7.3942
7.3680
7.1933
7.1654
6.9207
6.8924
6.8834
6.8580
6.5883
6.5654
5.1693
5.1455
4.7155
4.6910
4.6671
4.4599
4.4427
4.4313
4.4142
4.1361
3.6887
3.0664
3.0439
2.5566
2.1267
2.1090
2.1034
2.0861
2.0806
1.3186
1.2950
0.8754
0.8528
0.8472
0.8244
OMe
16k
0.90
0.88
1.03
2.89
1.97
0.96
0.91
0.99
1.03
1.03
1.16
3.00
2.03
3.03
1.07
9.63
3.44
7.07
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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138.9484
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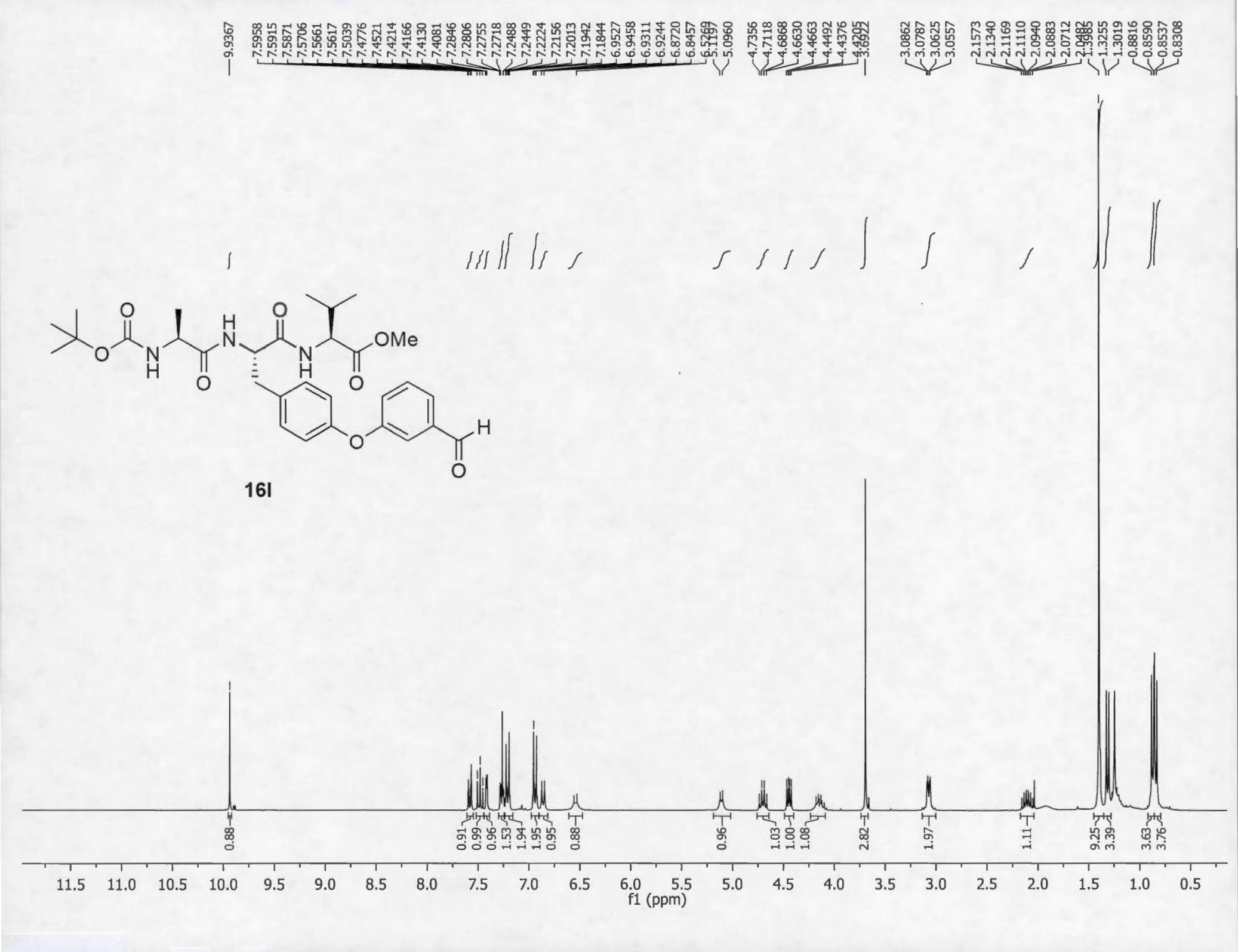
130.9809
130.0570
123.3431
123.2383
119.3917
118.0176
80.2948
57.4705
54.4984
52.2457
50.4230
37.4262
31.2772
28.3933
26.8539
24.8151
18.9890
18.3359
17.9240
OMe
16k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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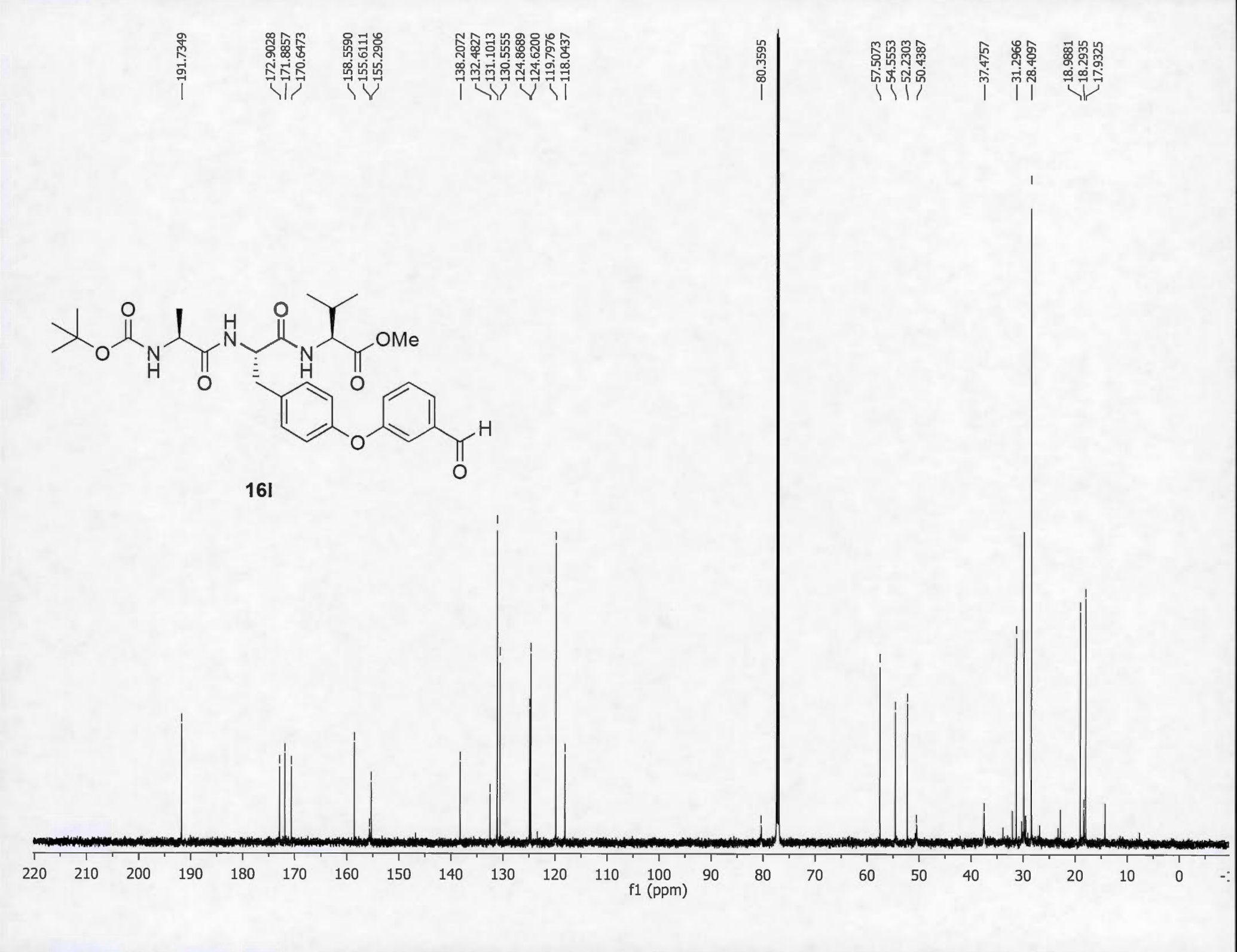
7.5617
7.5039
7.4776
7.4521
7.4214
7.4166
7.4130
7.4081
7.2846
7.2806
7.2755
7.2718
7.2488
7.2449
7.2224
7.2156
7.2013
7.1942
7.1844
6.9527
6.9458
6.9311
6.9244
6.8720
6.8457
5.1197
5.0960
4.7356
4.7118
4.6868
4.6630
4.4663
4.4492
4.4376
3.6922
3.0862
3.0787
3.0625
3.0557
2.1573
2.1340
2.1169
2.1110
2.0940
2.0883
2.0712
1.3255
1.3019
0.8816
0.8590
0.8537
0.8308
OMe
16l
0.88
0.91
0.99
0.96
1.53
1.94
1.95
0.95
0.88
0.96
1.03
1.00
1.08
2.82
1.97
1.11
9.25
3.39
3.63
3.76
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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132.4827
131.1013
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124.8689
124.6200
119.7976
118.0437
80.3595
57.5073
54.5553
52.2303
50.4387
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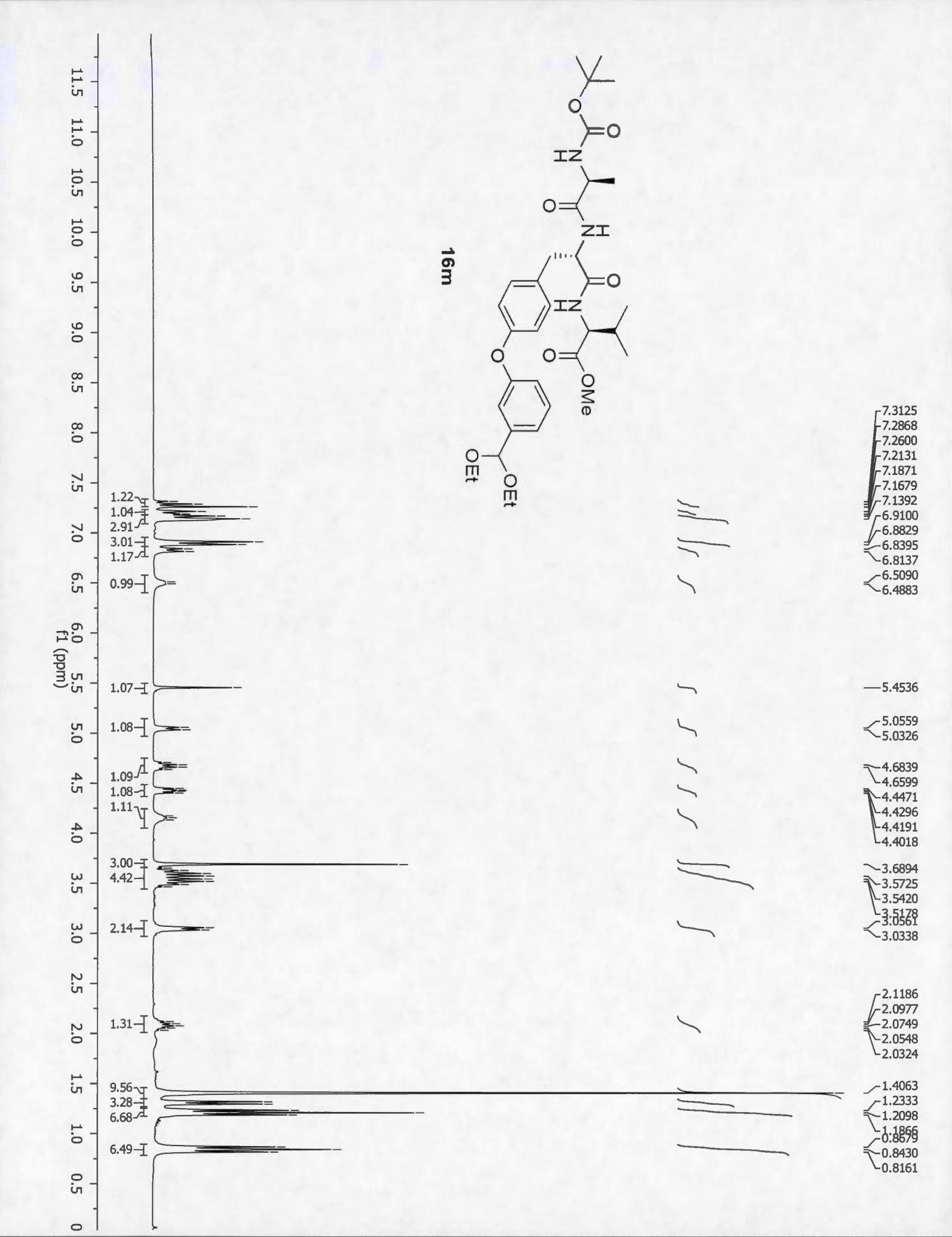
31.2966
28.4097
18.9881
18.2935
17.9325
OMe
H
16l
f1 (ppm)


16m
OMe
OEt
OEt
f1 (ppm)
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1.04
2.91
3.01
1.17
0.99
1.07
1.08
1.09
1.08
1.11
3.00
4.42
2.14
1.31
9.56
3.28
6.68
6.49
7.3125
7.2868
7.2600
7.2131
7.1871
7.1679
7.1392
6.9100
6.8829
6.8395
6.8137
6.5090
6.4883
5.4536
5.0559
5.0326
4.6839
4.6599
4.4471
4.4296
4.4191
4.4018
3.6894
3.5725
3.5420
3.5178
3.0561
3.0338
2.1186
2.0977
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2.0324
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1.2333
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1.1866
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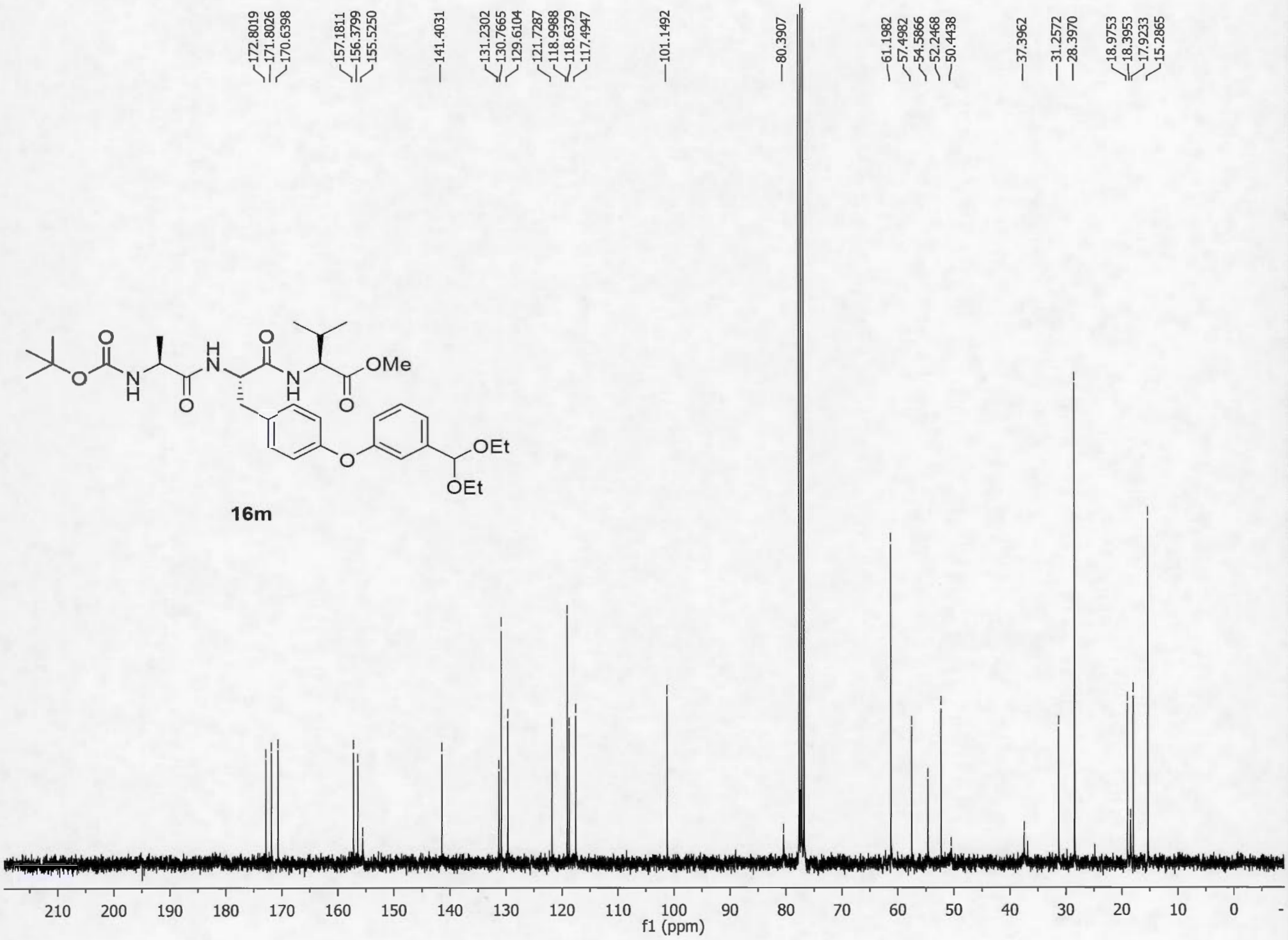
0.8161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141.4031
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130.7665
129.6104
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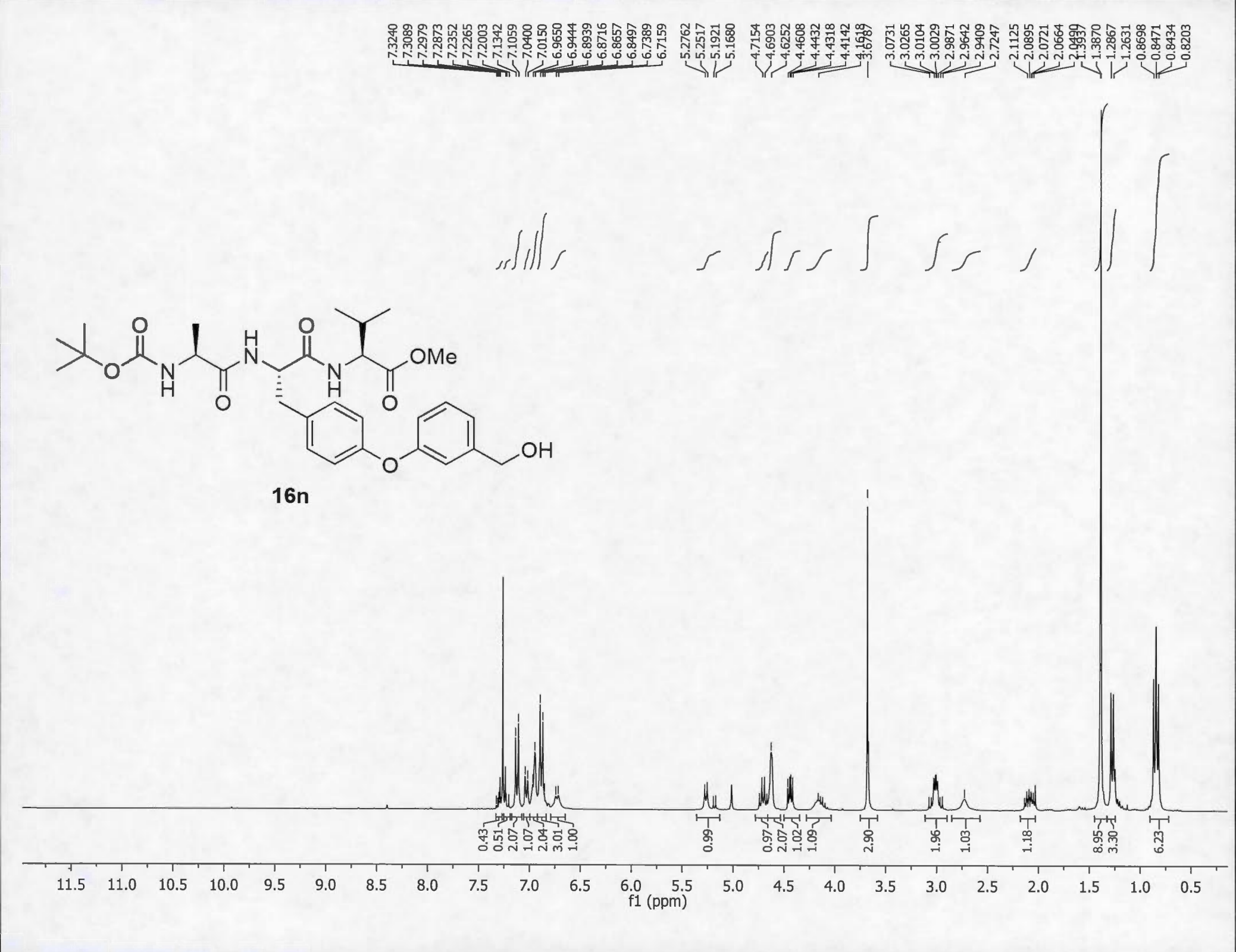
118.9988
118.6379
117.4947
101.1492
80.3907
61.1982
57.4982
54.5866
52.2468
50.4438
37.3962
31.2572
28.3970
18.9753
18.3953
17.9233
15.2865
OMe
OEt
OEt
16m
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.1059
7.0400
7.0150
6.9650
6.9444
6.8939
6.8716
6.8657
6.8497
6.7389
6.7159
5.2762
5.2517
5.1921
5.1680
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4.6903
4.6252
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4.4432
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4.1618
3.6787
3.0731
3.0265
3.0104
3.0029
2.9871
2.9642
2.9409
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2.0721
2.0664
2.0490
1.3937
1.3870
1.2867
1.2631
0.8698
0.8471
0.8434
0.8203
OMe
OH
16n
0.43
0.51
2.07
1.07
2.04
3.01
1.00
0.99
0.97
2.07
1.02
1.09
2.90
1.96
1.03
1.18
8.95
3.30
6.23
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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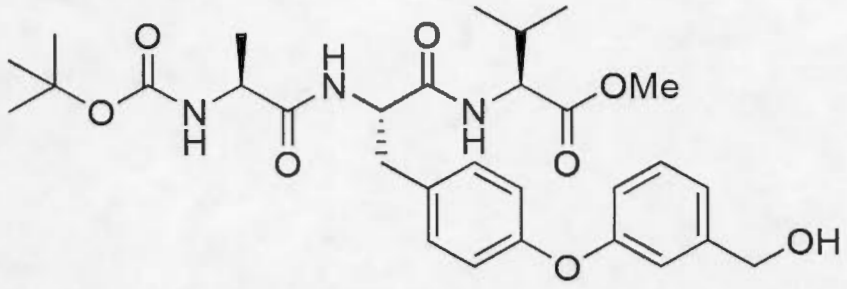
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


OMe
OH

16n

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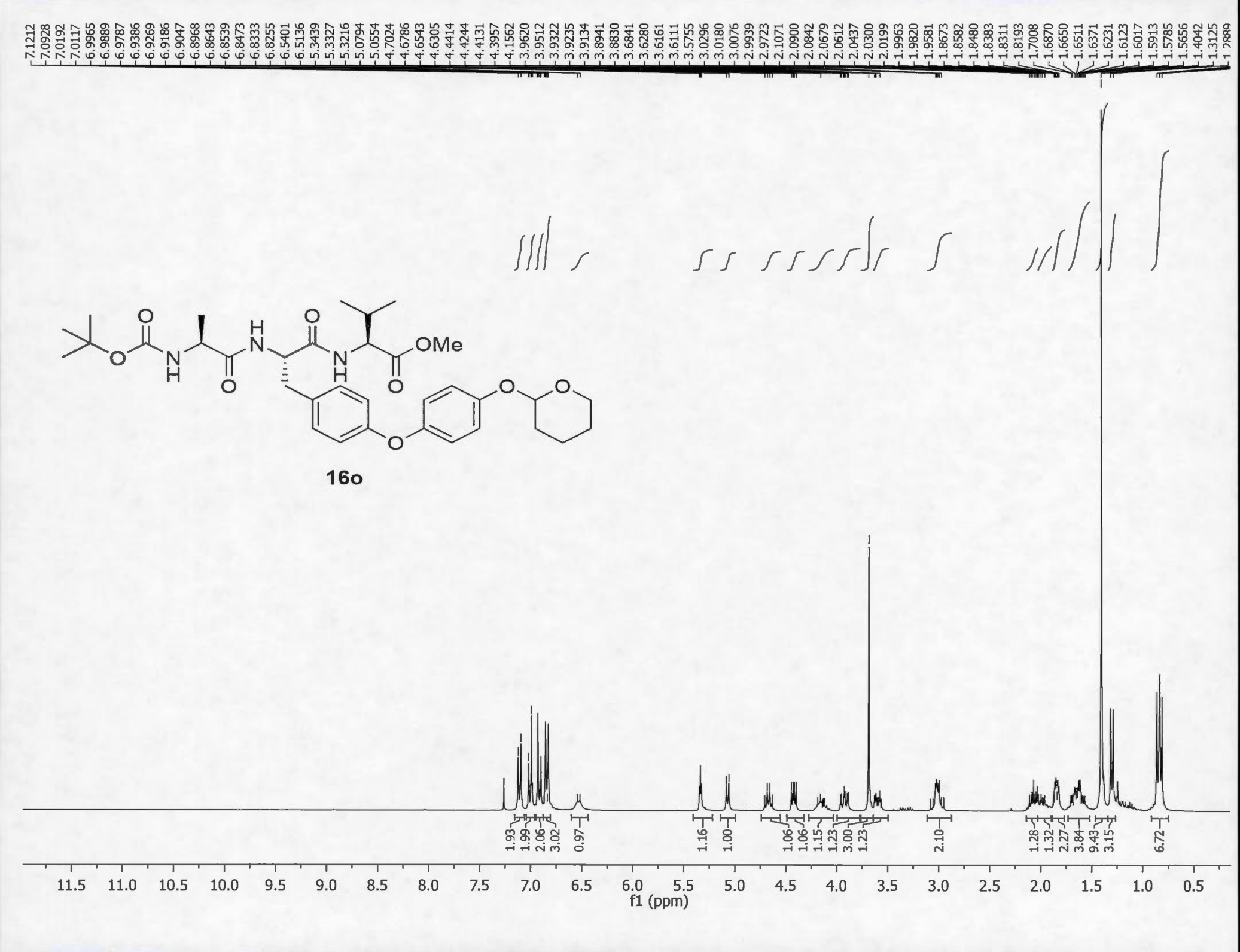
143.2776
131.5297
130.8097
129.8916
121.4498
119.4932
117.7697
116.6667
80.3285
64.8237
57.4832
54.5828
52.2960
50.3420
37.5360
31.3003
28.4058
18.9924
18.4603
17.9534
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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6.9386
6.9269
6.9186
6.9047
6.8968
6.8643
6.8539
6.8473
6.8333
6.8255
6.5401
6.5136
5.3439
5.3327
5.3216
5.0794
5.0554
4.7024
4.6786
4.6543
4.6305
4.4414
4.4244
4.4131
4.3957
4.1562
3.9620
3.9512
3.9322
3.9235
3.9134
3.8941
3.8830
3.6841
3.6280
3.6161
3.6111
3.5755
3.0296
3.0180
3.0076
2.9939
2.9723
2.1071
2.0900
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2.0612
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2.0300
2.0199
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1.8480
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1.8311
1.8193
1.7008
1.6870
1.6650
1.6511
1.6371
1.6231
1.6123
1.6017
1.5913
1.5785
1.5656
1.4042
1.3125
OMe
16o
1.93
1.99
2.06
3.02
0.97
1.16
1.00
1.06
1.06
1.15
1.23
3.00
1.23
2.10
1.28
1.32
2.27
3.84
9.43
3.15
6.72
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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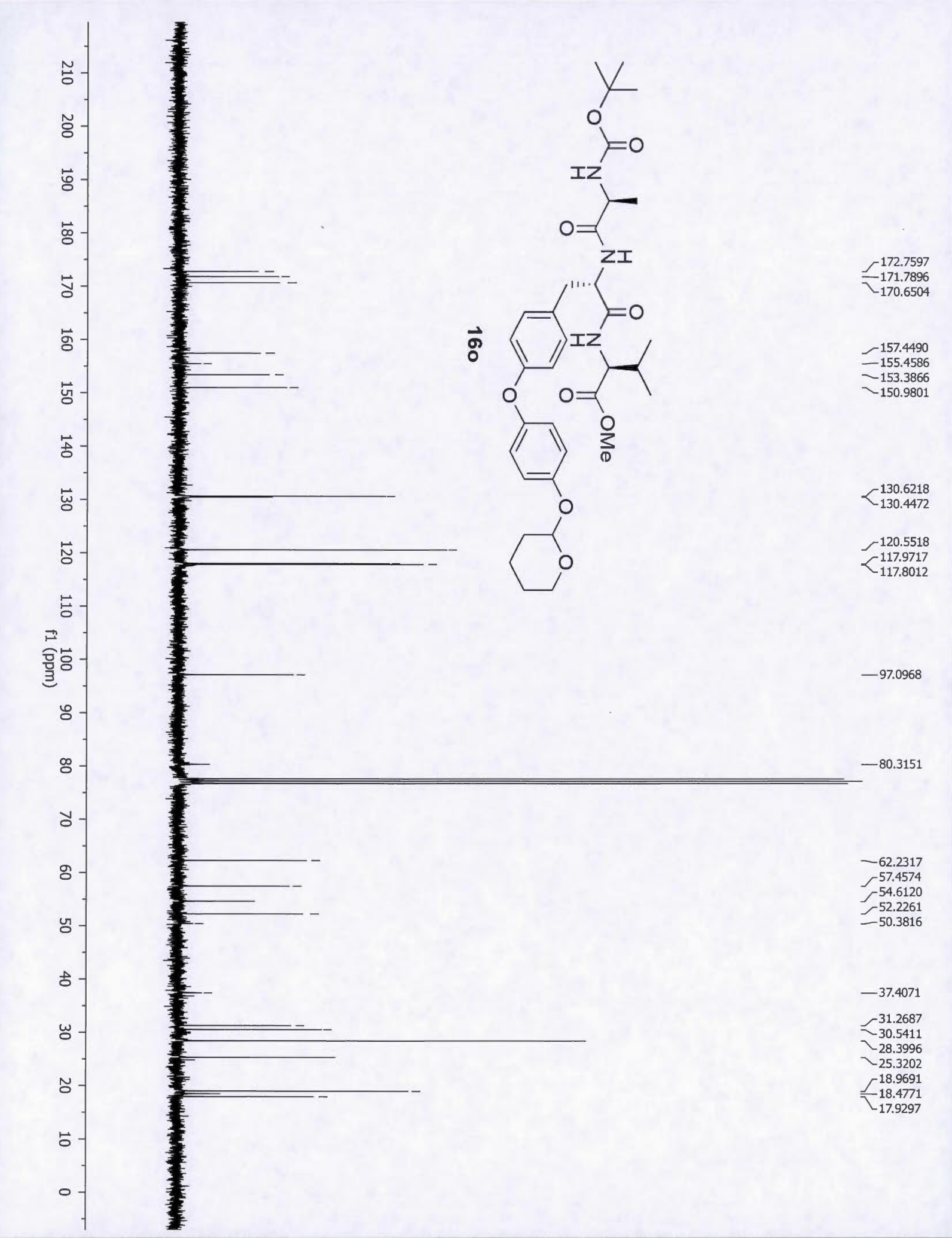
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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OMe
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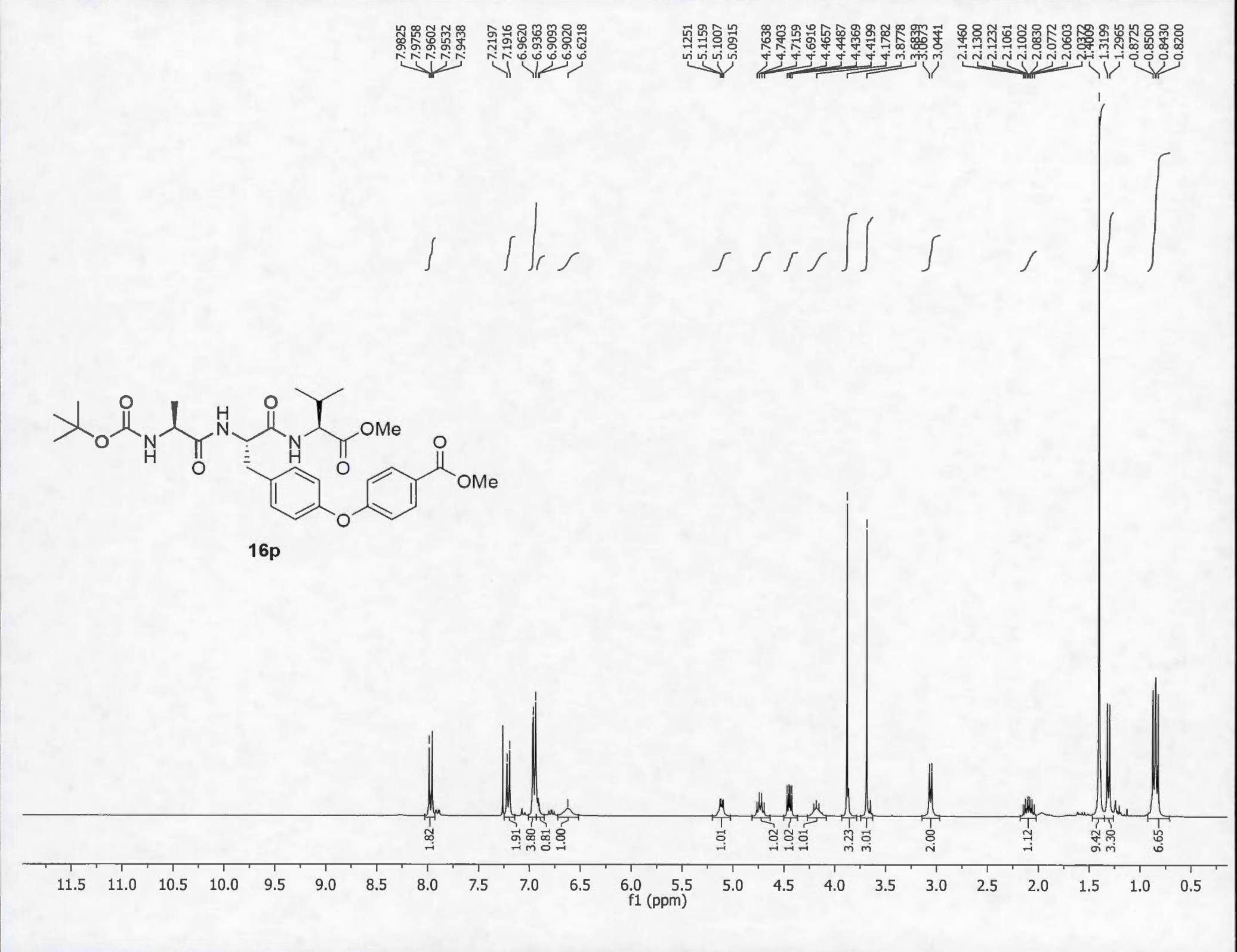
153.3866
150.9801
130.6218
130.4472
120.5518
117.9717
117.8012
97.0968
80.3151
62.2317
57.4574
54.6120
52.2261
50.3816
37.4071
31.2687
30.5411
28.3996
25.3202
18.9691
18.4771
17.9297
f1 (ppm)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7.9758
7.9602
7.9532
7.9438
7.2197
7.1916
6.9620
6.9363
6.9093
6.9020
6.6218
5.1251
5.1159
5.1007
5.0915
4.7638
4.7403
4.7159
4.6916
4.4657
4.4487
4.4369
4.4199
4.1782
3.8778
3.6839
3.6673
3.0441
2.1460
2.1300
2.1232
2.1061
2.1002
2.0830
2.0772
2.0603
1.3199
1.2965
0.8725
0.8500
0.8430
0.8200
OMe
OMe
16p
1.82
1.91
3.80
0.81
1.00
1.01
1.02
1.02
1.01
3.23
3.01
2.00
1.12
9.42
3.30
6.65
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

16p
172.8896
171.8634
170.6020
166.6977
161.8305
155.4931
154.6889
132.6876
131.7692
131.0760
124.5673
120.2566
117.3458
80.3251
57.4098
54.5734
52.2634
52.1228
50.3058
37.6085
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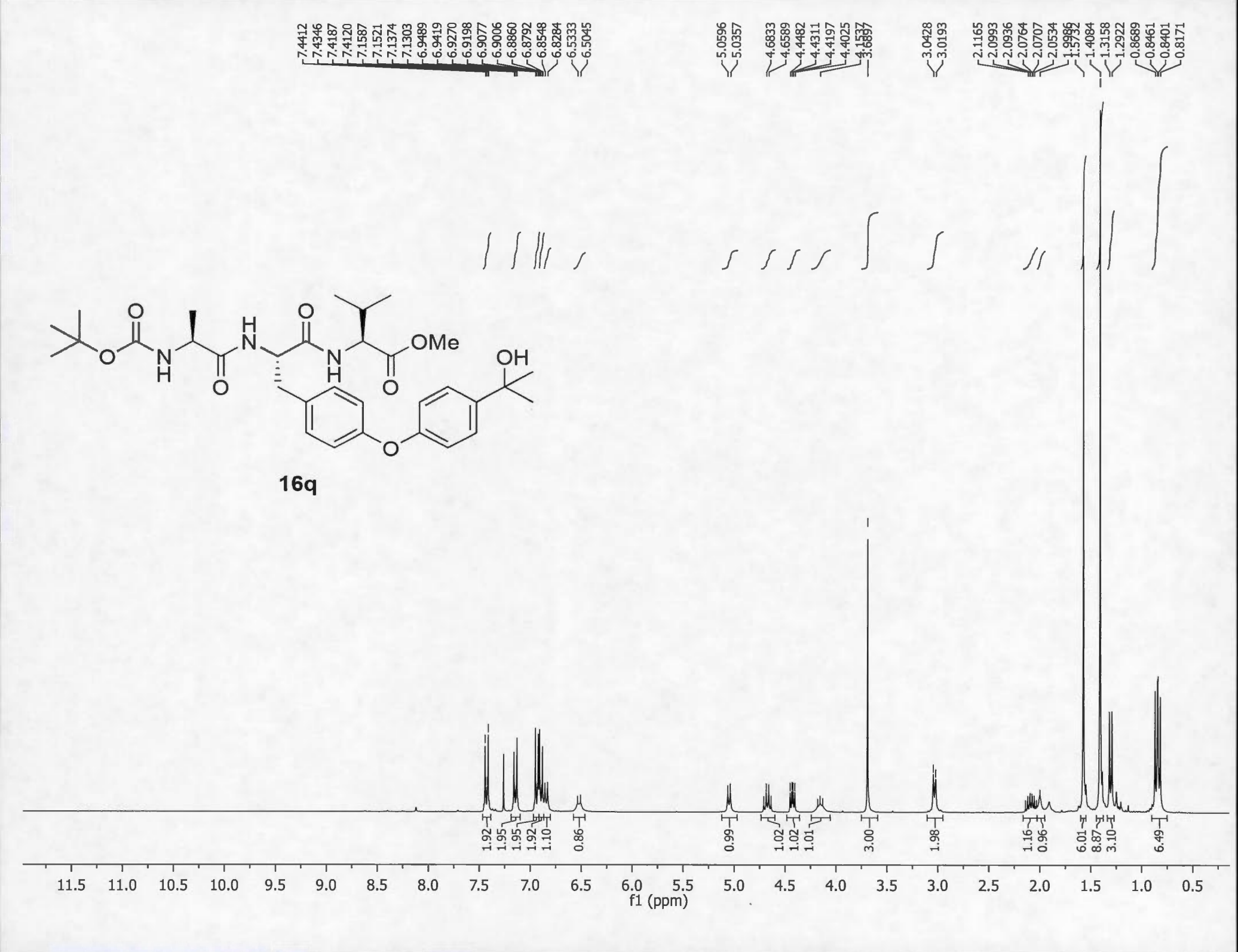
18.9817
18.4824
17.9072
f1 (ppm)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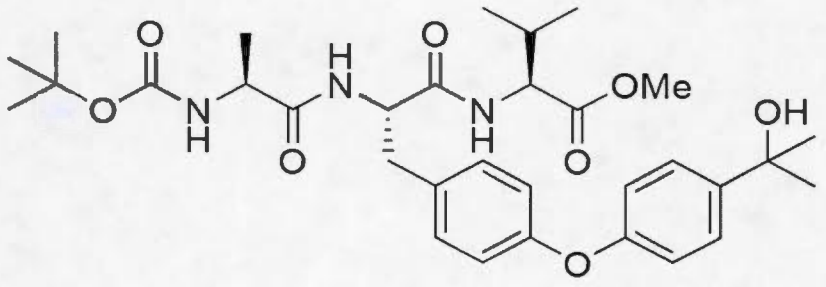
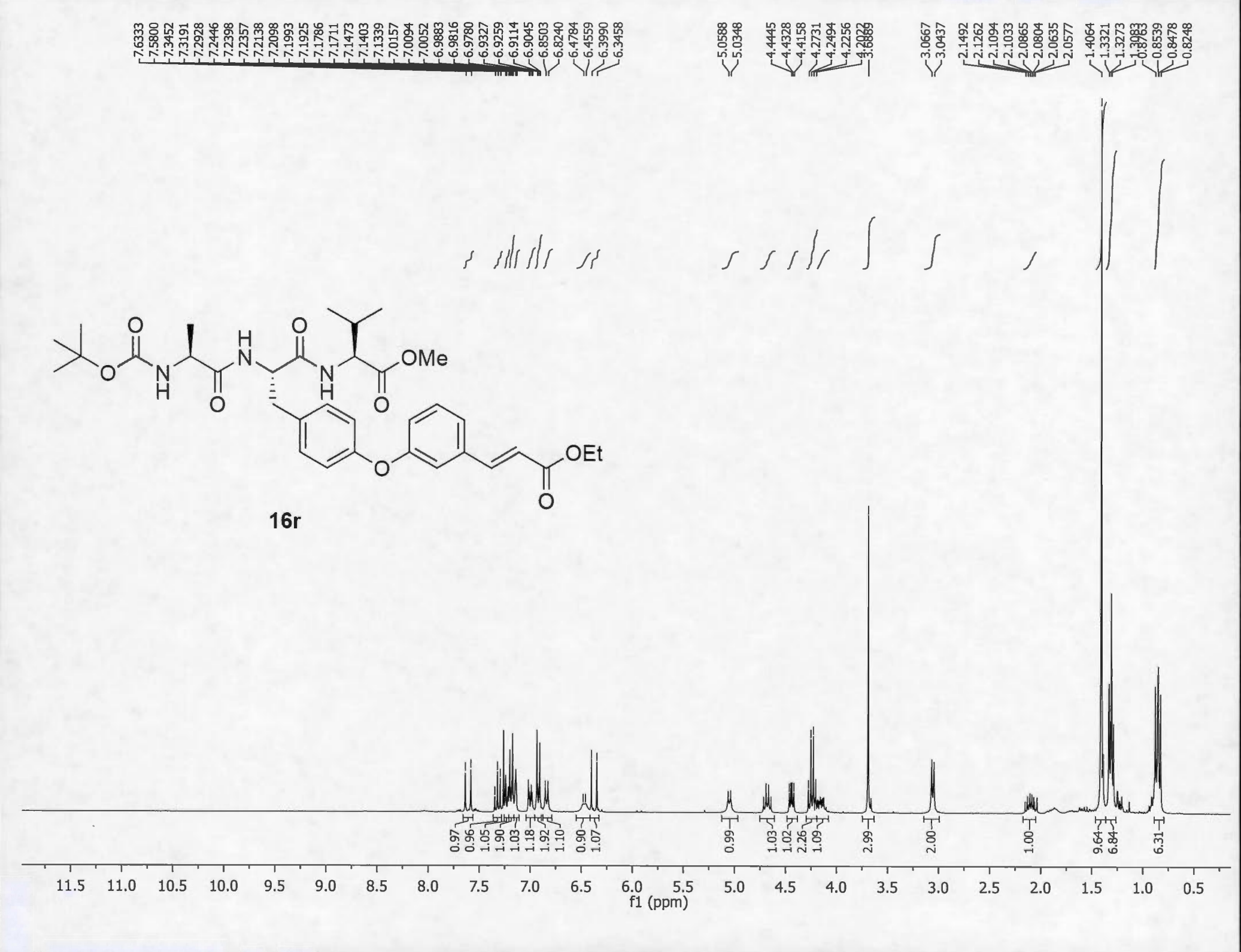
7.4346
7.4187
7.4120
7.1587
7.1521
7.1374
7.1303
6.9489
6.9419
6.9270
6.9198
6.9077
6.9006
6.8860
6.8792
6.8548
6.8284
6.5333
6.5045
5.0596
5.0357
4.6833
4.6589
4.4482
4.4311
4.4197
4.4025
4.1537
3.6897
3.0428
3.0193
2.1165
2.0993
2.0936
2.0764
2.0707
2.0534
1.9986
1.5732
1.4084
1.3158
1.2922
0.8689
0.8461
0.8401
0.8171
OMe
OH
16q
1.92
1.95
1.95
1.92
1.10
0.86
0.99
1.02
1.02
1.01
3.00
1.98
1.16
0.96
6.01
8.87
3.10
6.49
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


O
O
N
H
O
HN
O
N
H
OMe
O
OH
O

16q

172.8048
171.8225
170.6421
156.4642
155.8771
155.4669
144.2350
131.1631
130.7428
126.0282
118.9662
118.5440
80.3958
72.3610
57.4775
54.6310
52.2625
50.4213
37.4318
31.9503
31.2905
28.4126
18.9835
18.4787
17.9357
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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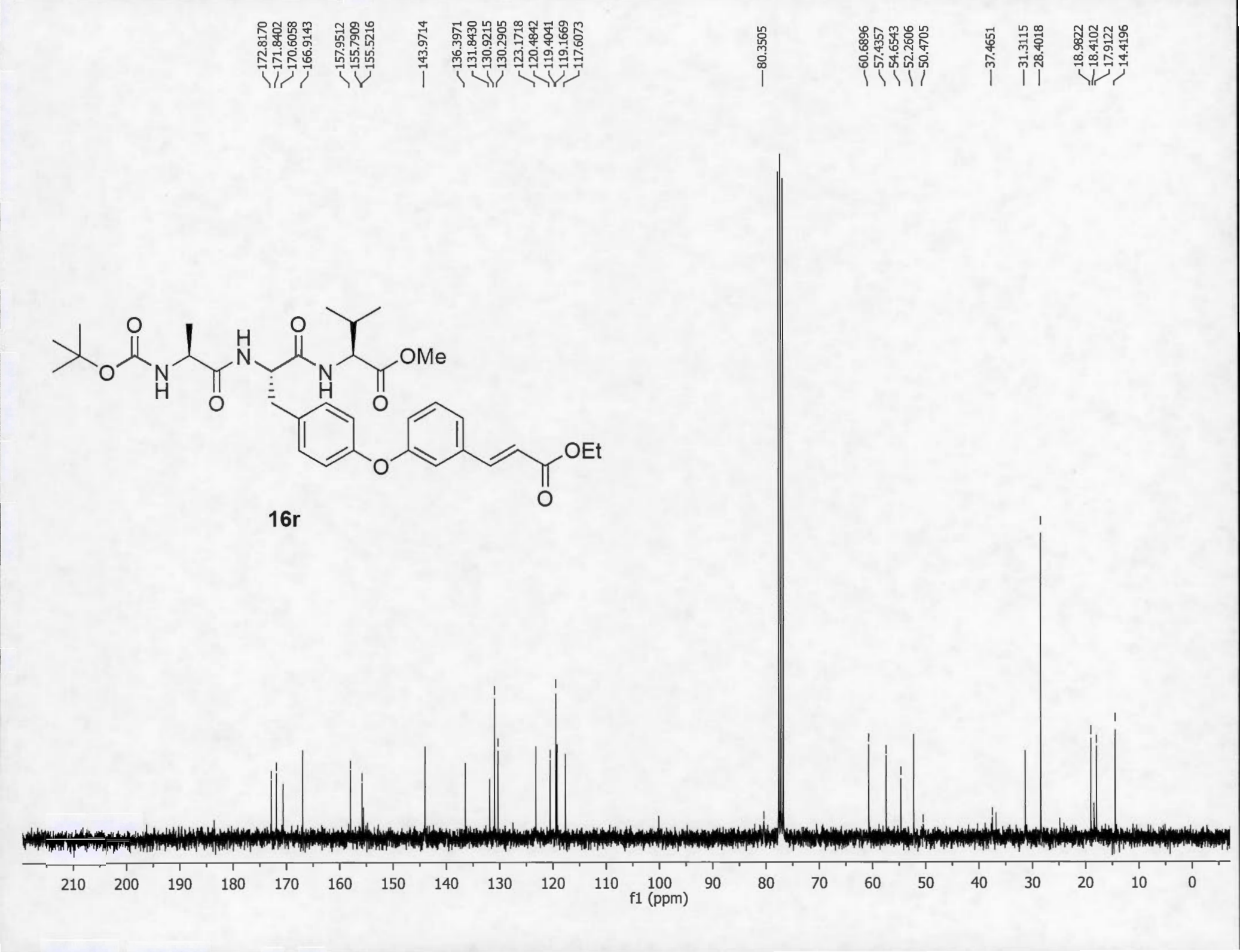
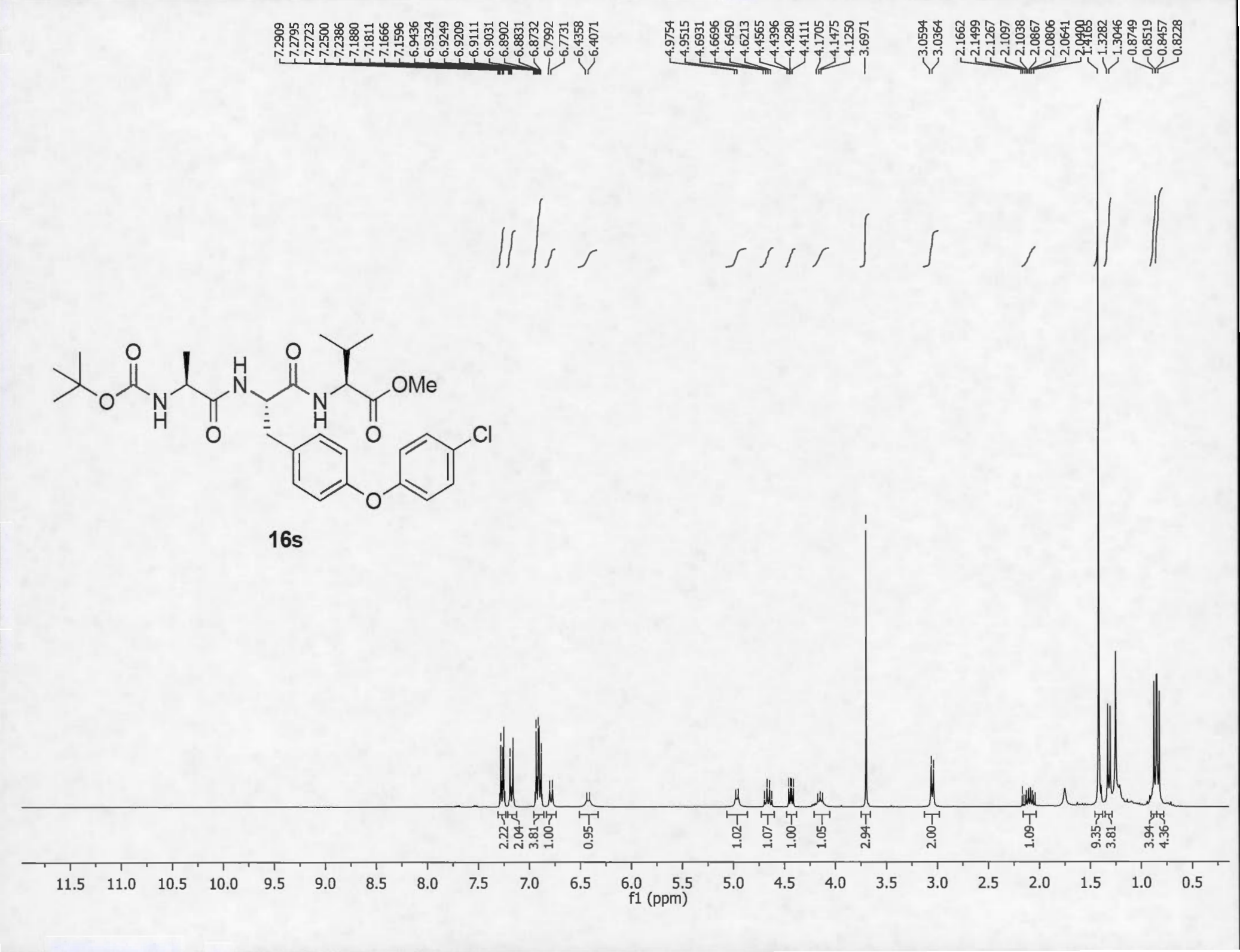
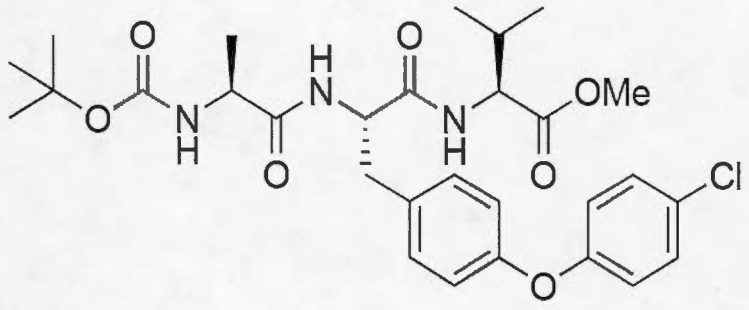
7.5800
7.3452
7.3191
7.2928
7.2446
7.2398
7.2357
7.2138
7.2098
7.1993
7.1925
7.1786
7.1711
7.1473
7.1403
7.1339
7.0157
7.0094
7.0052
6.9883
6.9816
6.9780
6.9327
6.9259
6.9114
6.9045
6.8503
6.8240
6.4784
6.4559
6.3990
6.3458
5.0588
5.0348
4.4445
4.4328
4.4158
4.2731
4.2494
4.2256
4.2022
3.0667
3.0437
2.1492
2.1262
2.1094
2.1033
2.0865
2.0804
2.0635
2.0577
1.4064
1.3321
1.3273
1.3083
0.8763
0.8539
0.8478
0.8248
OMe
OEt
O
N
H
0.97
0.96
1.05
1.90
1.03
1.18
1.92
1.10
0.90
1.07
0.99
1.03
1.02
2.26
1.09
2.99
2.00
1.00
9.64
6.84
6.31
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

16r

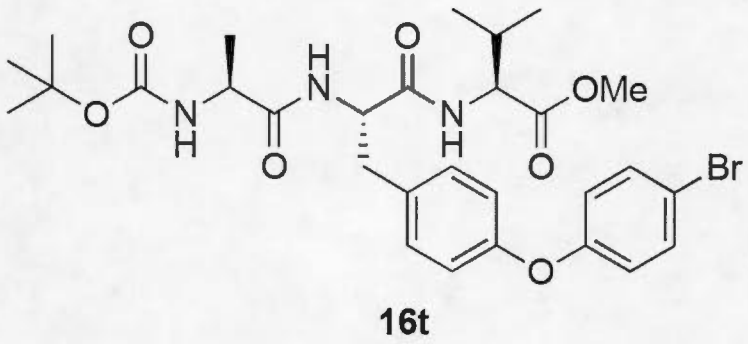

172.8170
171.8402
170.6058
166.9143
157.9512
155.7909
155.5216
143.9714
136.3971
131.8430
130.9215
130.2905
123.1718
120.4842
119.4041
119.1669
117.6073
80.3505
60.6896
57.4357
54.6543
52.2606
50.4705
37.4651
31.3115
28.4018
18.9822
18.4102
17.9122
14.4196
OMe
OEt
16r
f1 (ppm)


7.2909
7.2795
7.2723
7.2500
7.2386
7.1880
7.1811
7.1666
7.1596
6.9436
6.9324
6.9249
6.9209
6.9111
6.9031
6.8902
6.8831
6.8732
6.7992
6.7731
6.4358
6.4071
4.9754
4.9515
4.6931
4.6696
4.6450
4.6213
4.4565
4.4396
4.4280
4.4111
4.1705
4.1475
4.1250
3.6971
3.0594
3.0364
2.1662
2.1499
2.1267
2.1097
2.1038
2.0867
2.0806
2.0641
1.4165
1.3282
1.3046
0.8749
0.8519
0.8457
0.8228
OMe
Cl
16s
2.22
2.04
3.81
1.00
0.95
1.02
1.07
1.00
1.05
2.94
2.00
1.09
9.35
3.81
3.94
4.36
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


O
O
H
N
O
N
H
OMe
O
O
Cl

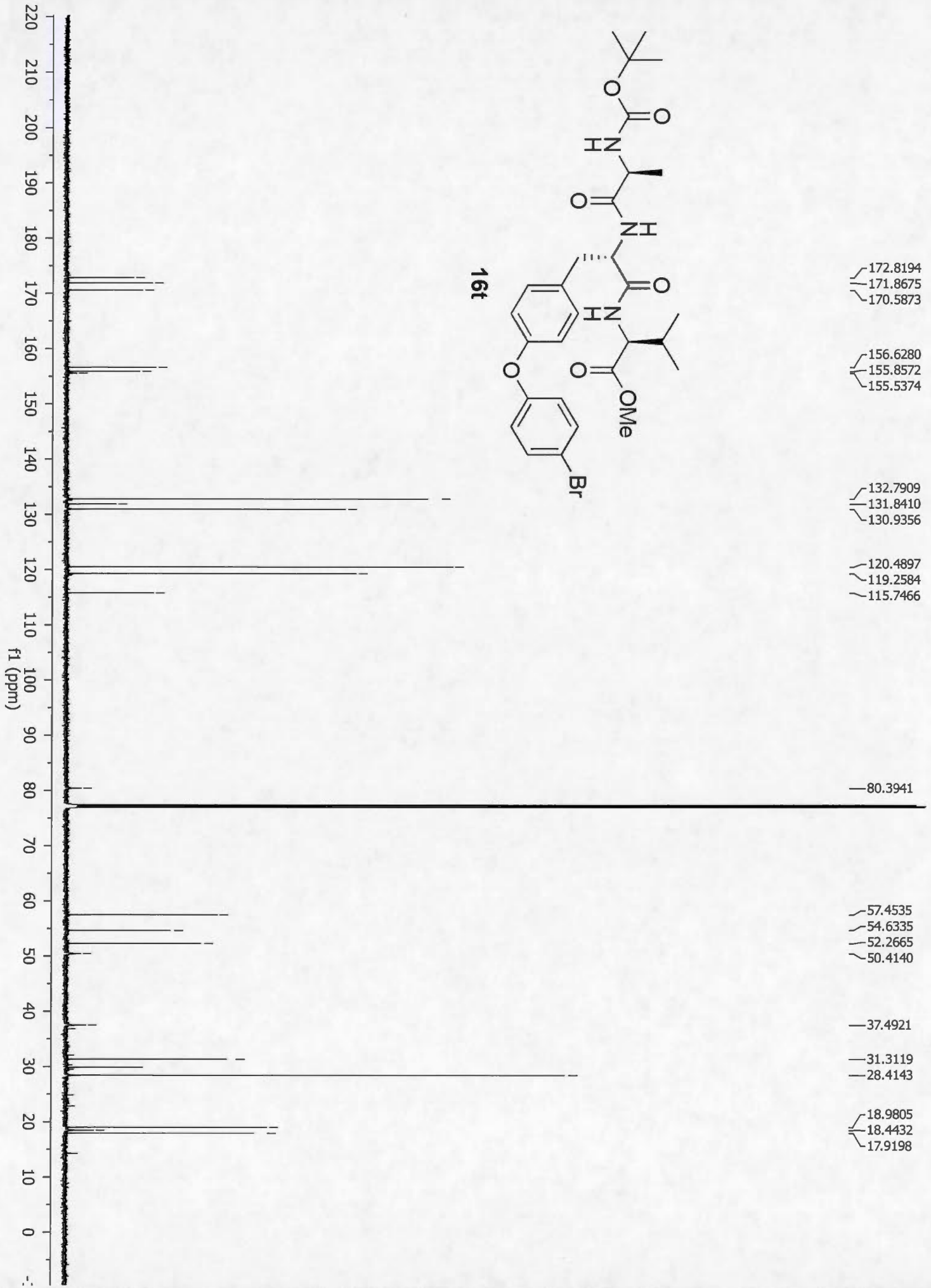
16s

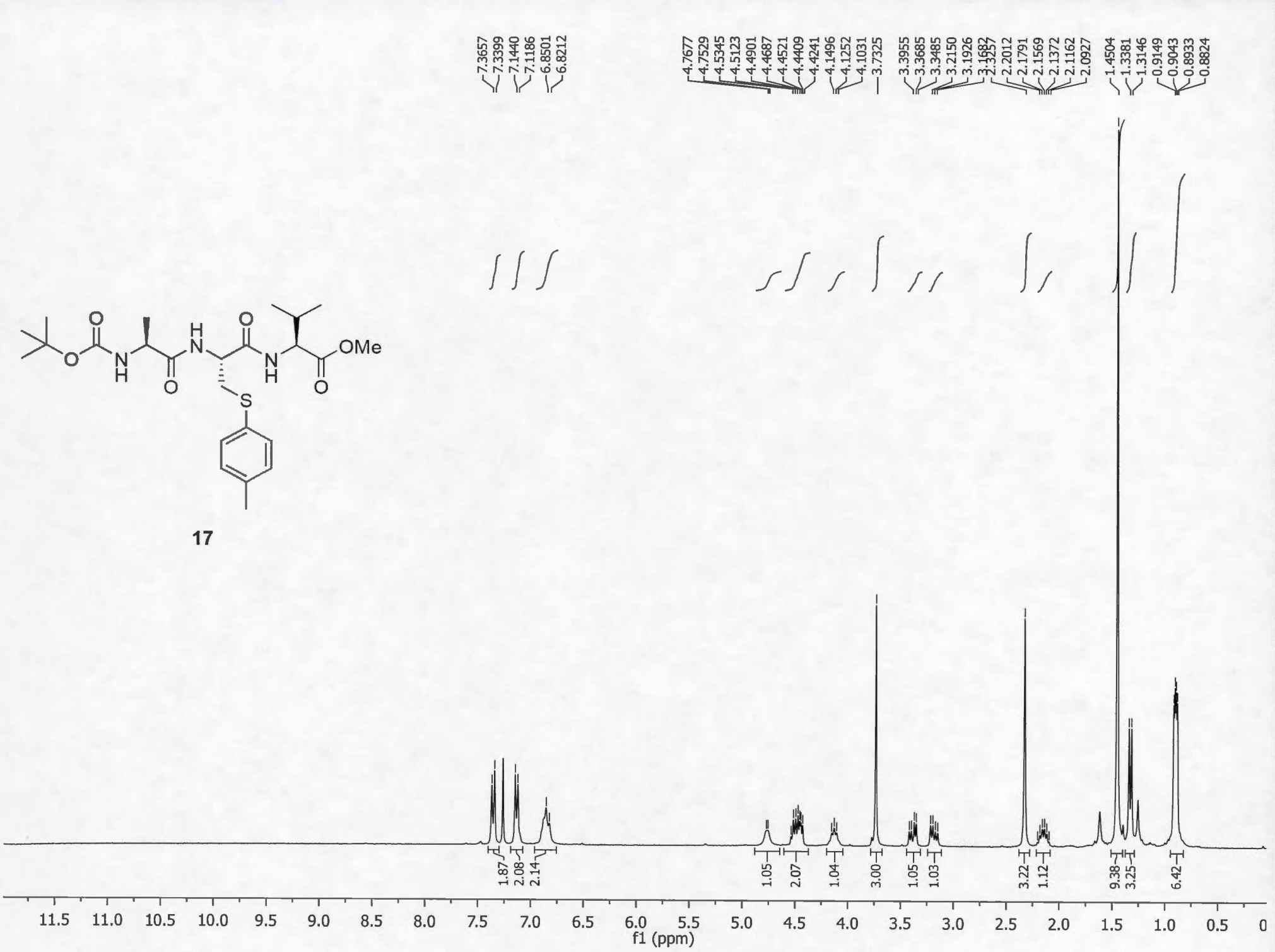
172.7625
171.8526
170.5343
156.0460
156.0258
155.5559
131.7409
130.9159
129.8448
128.3708
120.1156
119.1895
80.4596
57.4695
54.6583
52.2780
50.4128
37.4635
31.3191
28.4180
18.9856
18.3999
17.9184
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

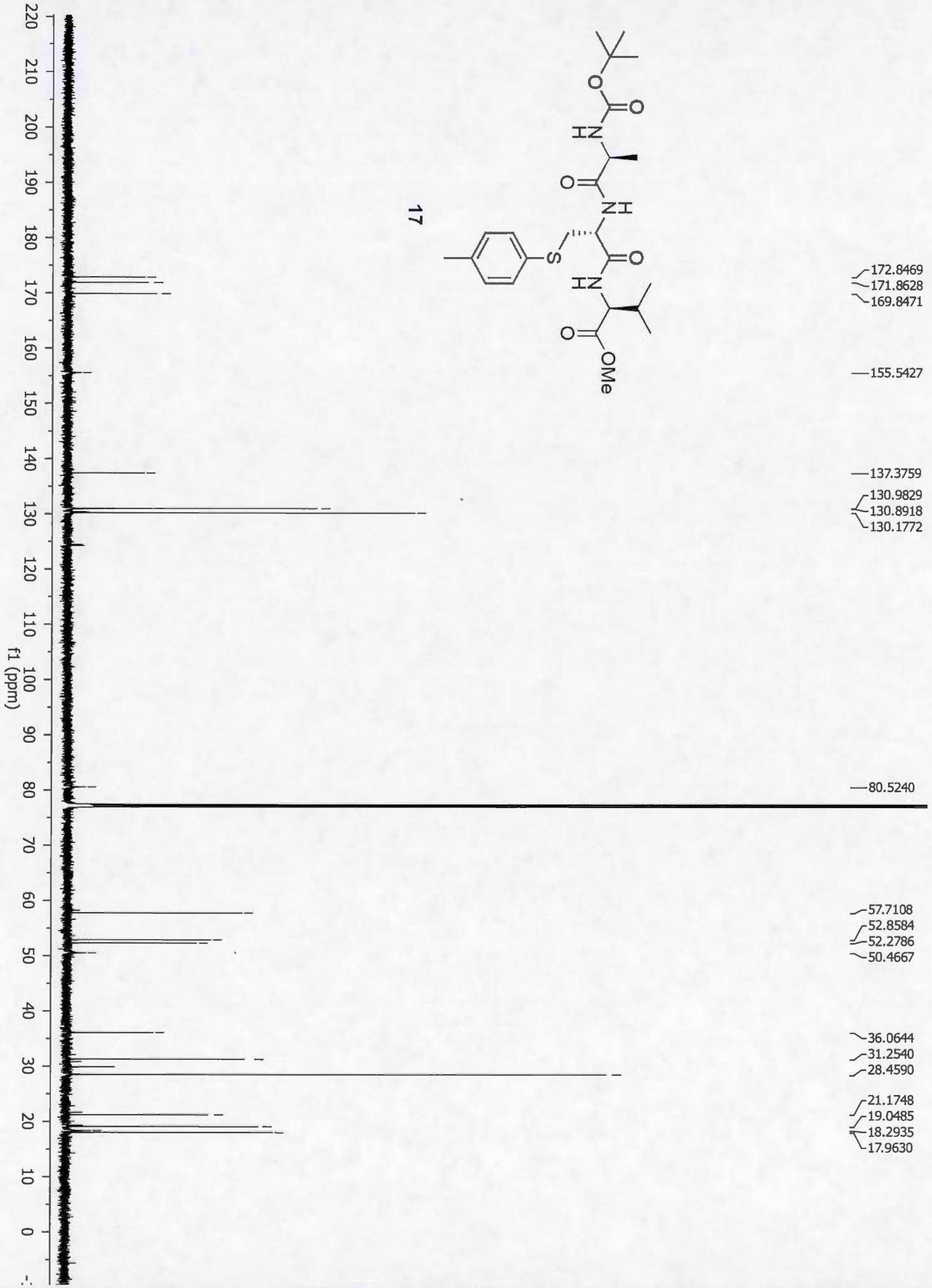

OMe
Br

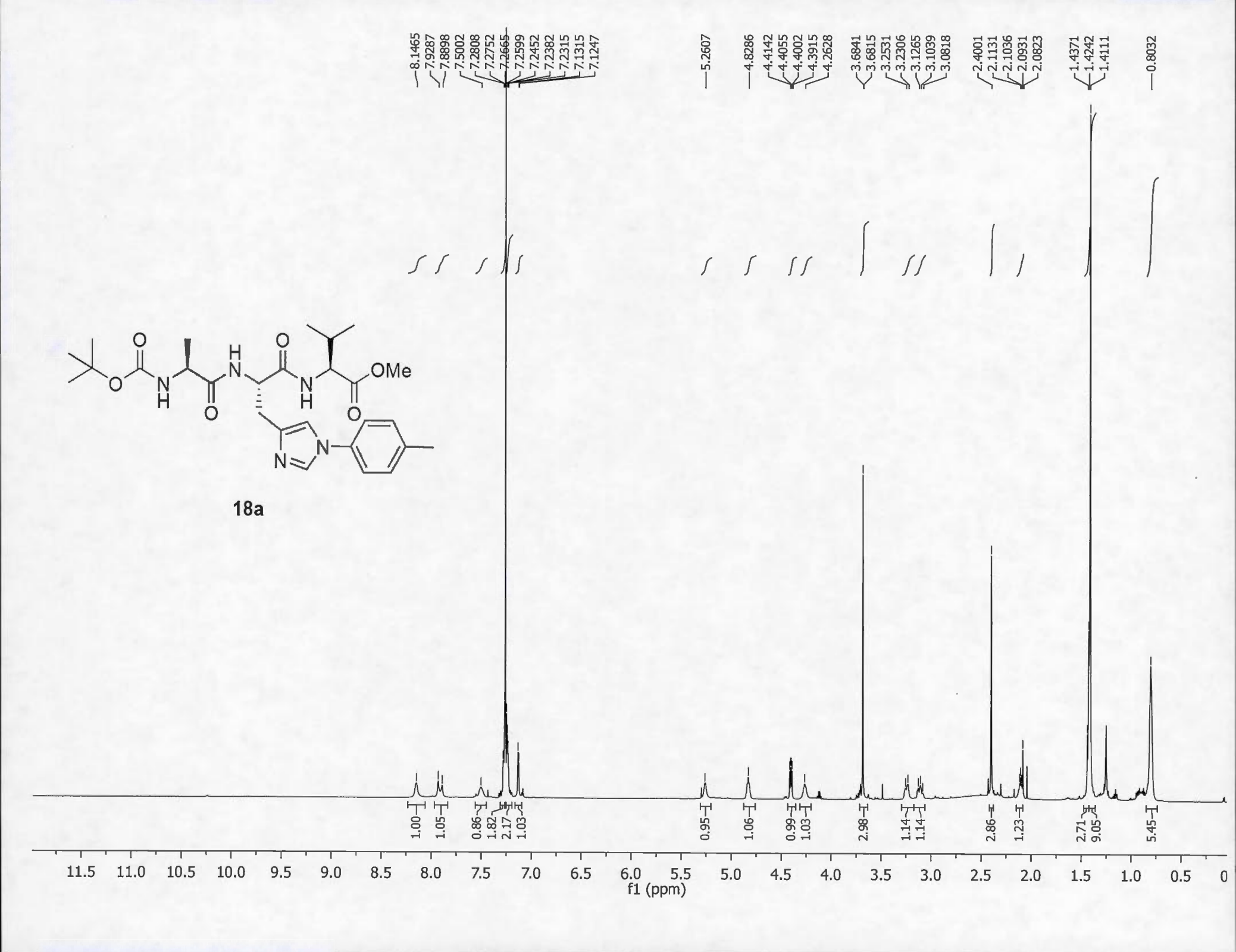
16t

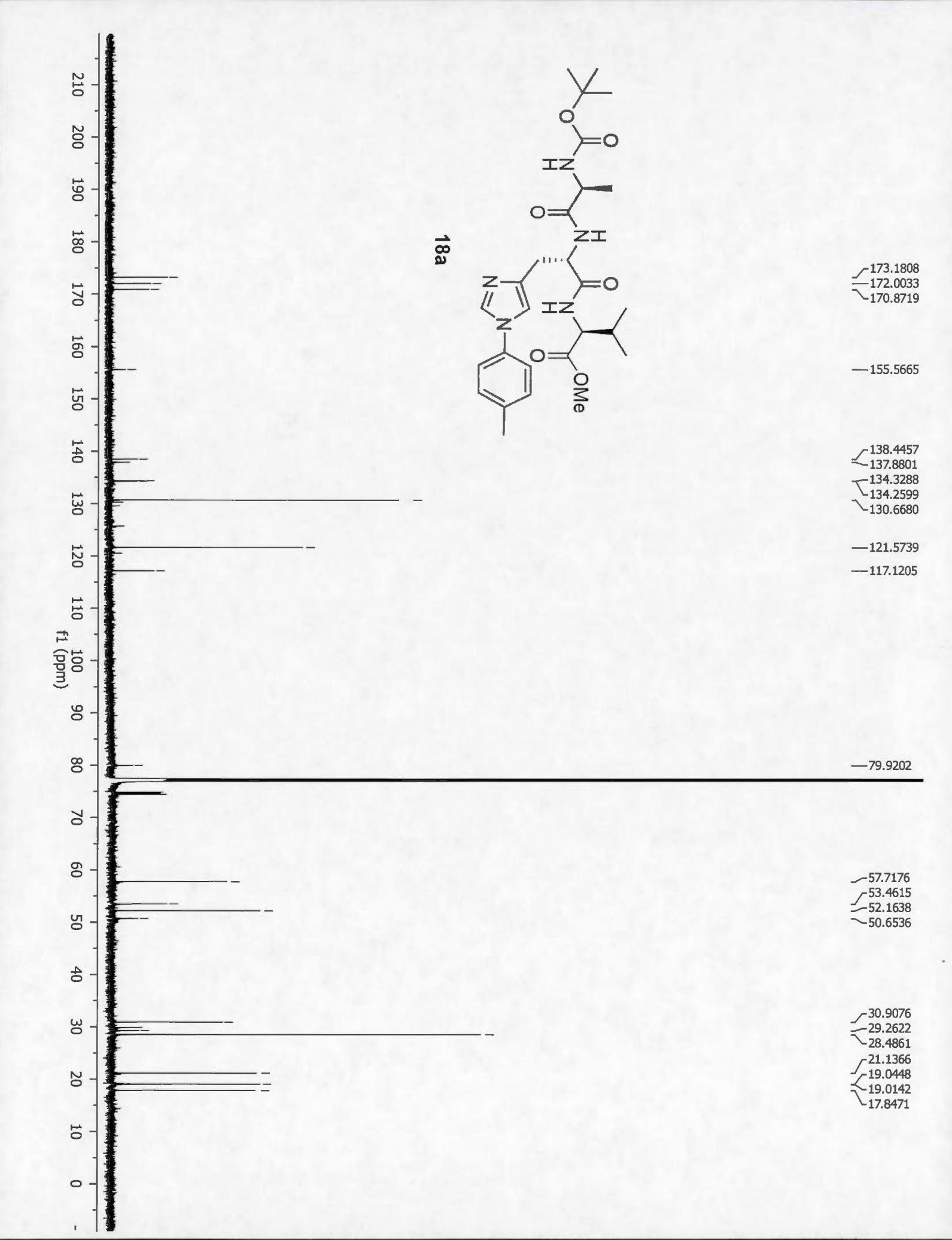
7.4302
7.4191
7.4123
7.3964
7.3894
7.3784
7.1964
7.1864
7.1794
7.1650
7.1578
7.1478
6.9116
6.9048
6.8893
6.8830
6.8762
6.8691
6.8538
6.8468
6.8190
6.7928
6.4689
6.4401
4.9991
4.9753
4.7027
4.6791
4.6546
4.6306
4.4569
4.4399
4.4281
4.4110
4.1742
4.1506
4.1269
3.6946
3.0560
3.0331
2.1306
2.1247
2.1076
2.1017
2.0847
2.0786
2.0619
1.4138
1.3256
1.3018
0.8733
0.8506
0.8440
0.8210
1.76
1.95
3.69
1.04
0.93
1.02
1.04
1.00
1.05
2.96
1.99
1.06
8.99
3.17
3.29
3.47
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

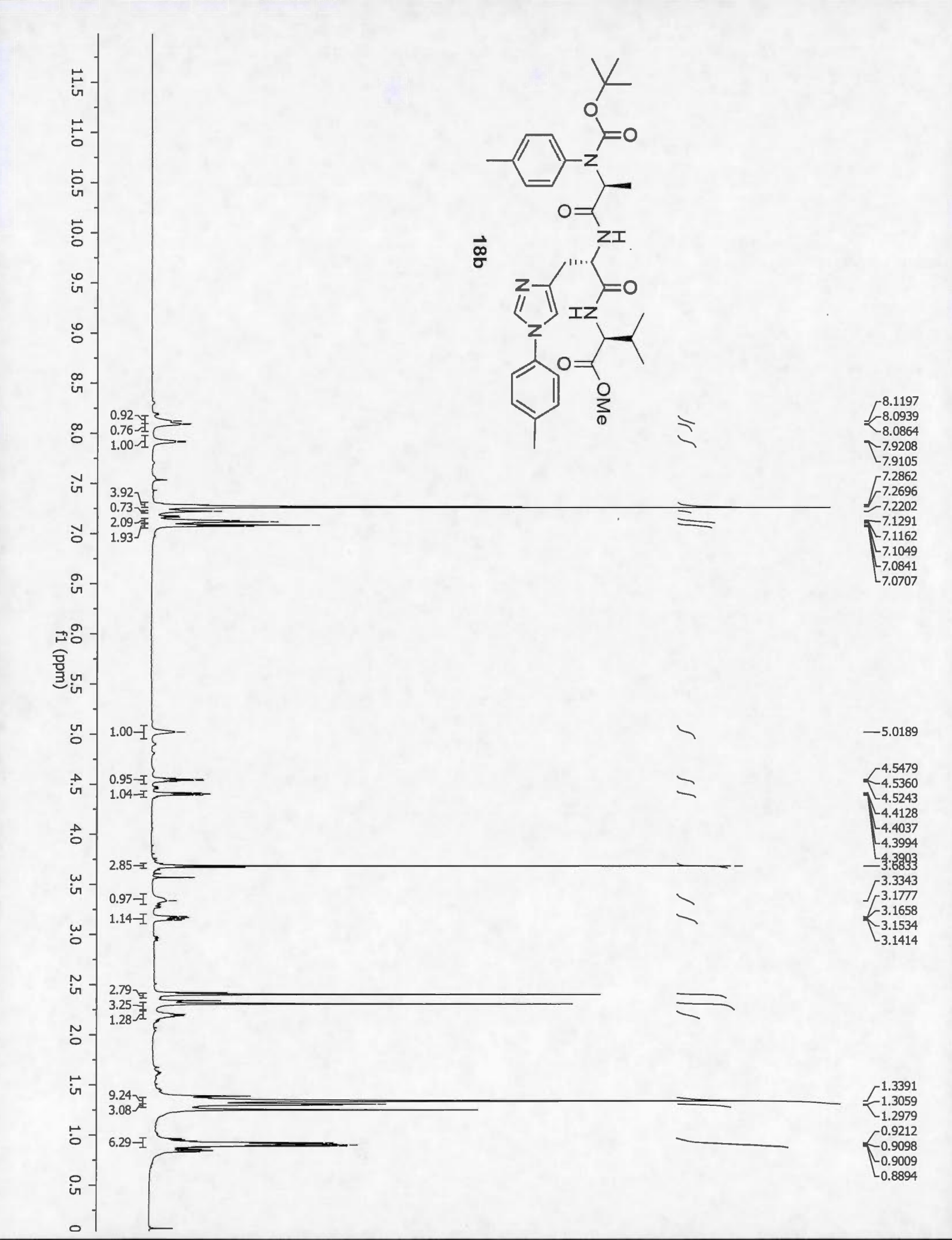

16t
172.8194
171.8675
170.5873
156.6280
155.8572
155.5374
132.7909
131.8410
130.9356
120.4897
119.2584
115.7466
80.3941
57.4535
54.6335
52.2665
50.4140
37.4921
31.3119
28.4143
18.9805
18.4432
17.9198
f1 (ppm)

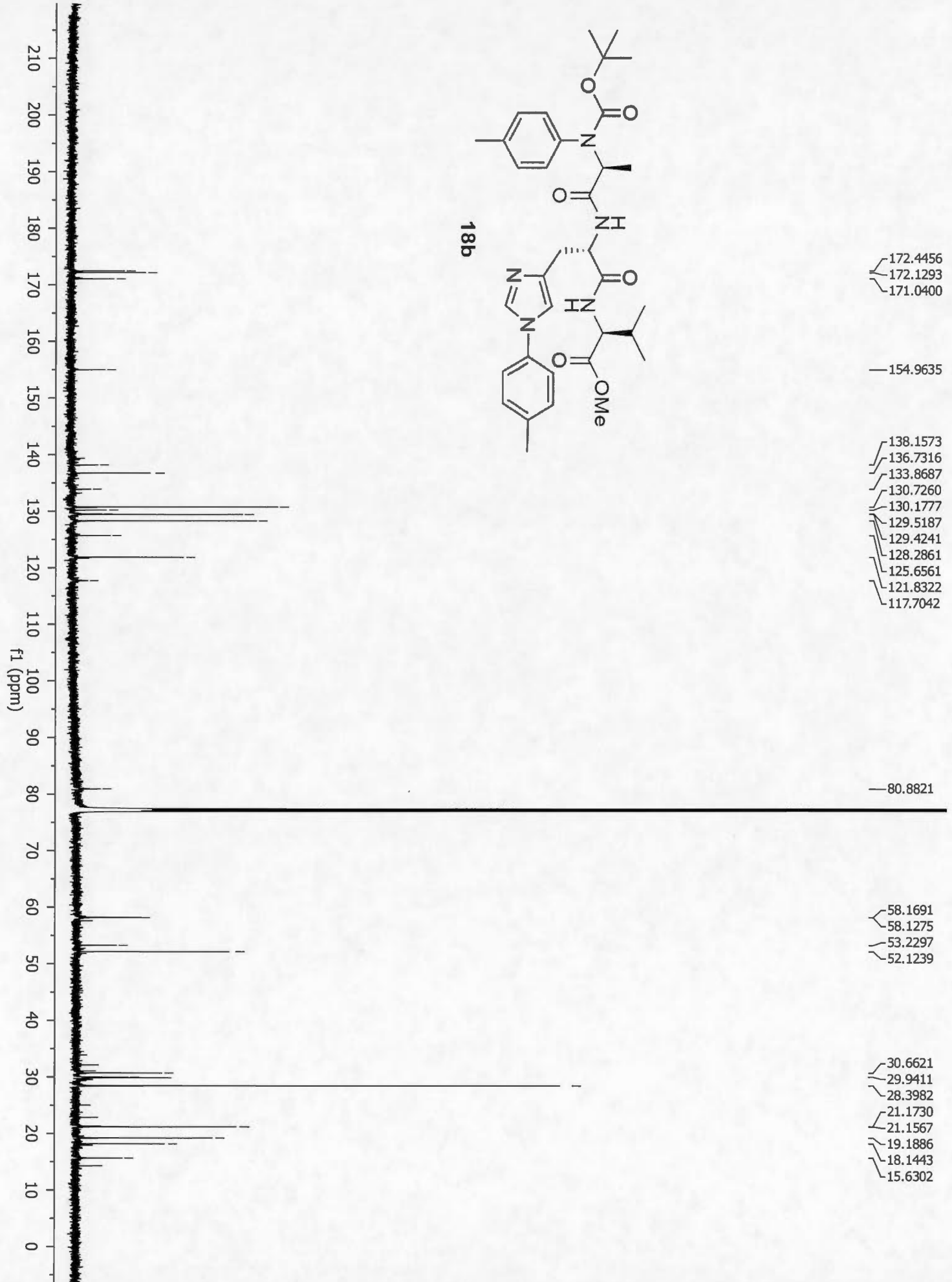

7.3657
7.3399
7.1440
7.1186
6.8501
6.8212
4.7677
4.7529
4.5345
4.5123
4.4901
4.4687
4.4521
4.4409
4.4241
4.1496
4.1252
4.1031
3.7325
3.3955
3.3685
3.3485
3.2150
3.1926
3.1682
2.2012
2.1791
2.1569
2.1372
2.1162
2.0927
1.4504
1.3381
1.3146
0.9149
0.9043
0.8933
0.8824
OMe
17
1.87
2.08
2.14
1.05
2.07
1.04
3.00
1.05
1.03
3.22
1.12
9.38
3.25
6.42
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

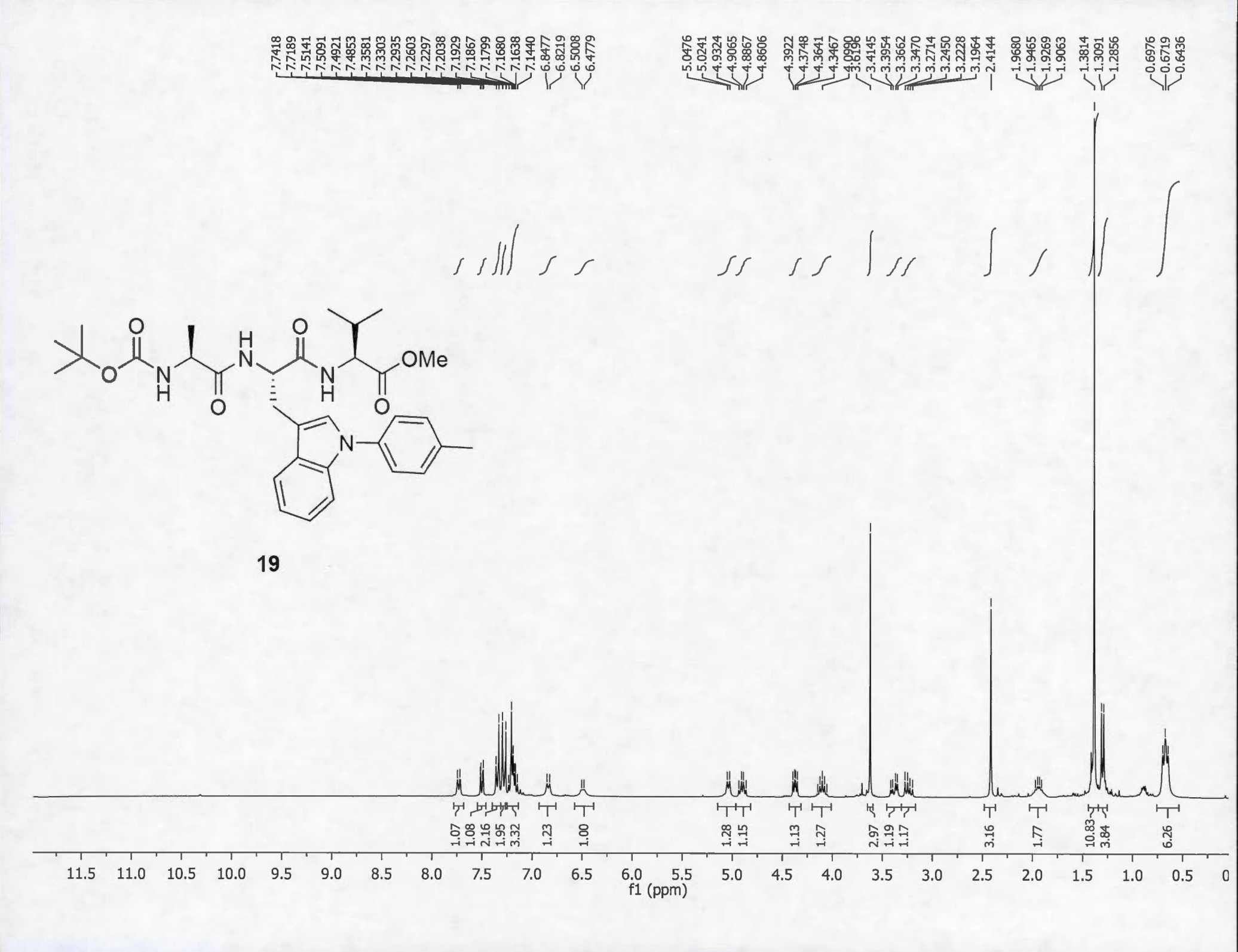

17
OMe
172.8469
171.8628
169.8471
155.5427
137.3759
130.9829
130.8918
130.1772
80.5240
57.7108
52.8584
52.2786
50.4667
36.0644
31.2540
28.4590
21.1748
19.0485
18.2935
17.9630
f1 (ppm)


8.1465
7.9287
7.8898
7.5002
7.2808
7.2752
7.2665
7.2599
7.2452
7.2382
7.2315
7.1315
7.1247
5.2607
4.8286
4.4142
4.4055
4.4002
4.3915
4.2628
3.6841
3.6815
3.2531
3.2306
3.1265
3.1039
3.0818
2.4001
2.1131
2.1036
2.0931
2.0823
1.4371
1.4242
1.4111
0.8032
OMe
18a
1.00
1.05
0.86
1.82
2.17
1.03
0.95
1.06
0.99
1.03
2.98
1.14
1.14
2.86
1.23
2.71
9.05
5.45
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


18a
OMe
173.1808
172.0033
170.8719
155.5665
138.4457
137.8801
134.3288
134.2599
130.6680
121.5739
117.1205
79.9202
57.7176
53.4615
52.1638
50.6536
30.9076
29.2622
28.4861
21.1366
19.0448
19.0142
17.8471
f1 (ppm)


18b
f1 (ppm)
0.92
0.76
1.00
3.92
0.73
2.09
1.93
1.00
0.95
1.04
2.85
0.97
1.14
2.79
3.25
1.28
9.24
3.08
6.29
8.1197
8.0939
8.0864
7.9208
7.9105
7.2862
7.2696
7.2202
7.1291
7.1162
7.1049
7.0841
7.0707
5.0189
4.5479
4.5360
4.5243
4.4128
4.4037
4.3994
4.3903
3.6833
3.3343
3.1777
3.1658
3.1534
3.1414
1.3391
1.3059
1.2979
0.9212
0.9098
0.9009
0.8894


18b
172.4456
172.1293
171.0400
154.9635
138.1573
136.7316
133.8687
130.7260
130.1777
129.5187
129.4241
128.2861
125.6561
121.8322
117.7042
80.8821
58.1691
58.1275
53.2297
52.1239
30.6621
29.9411
28.3982
21.1730
21.1567
19.1886
18.1443
15.6302
f1 (ppm)


7.7418
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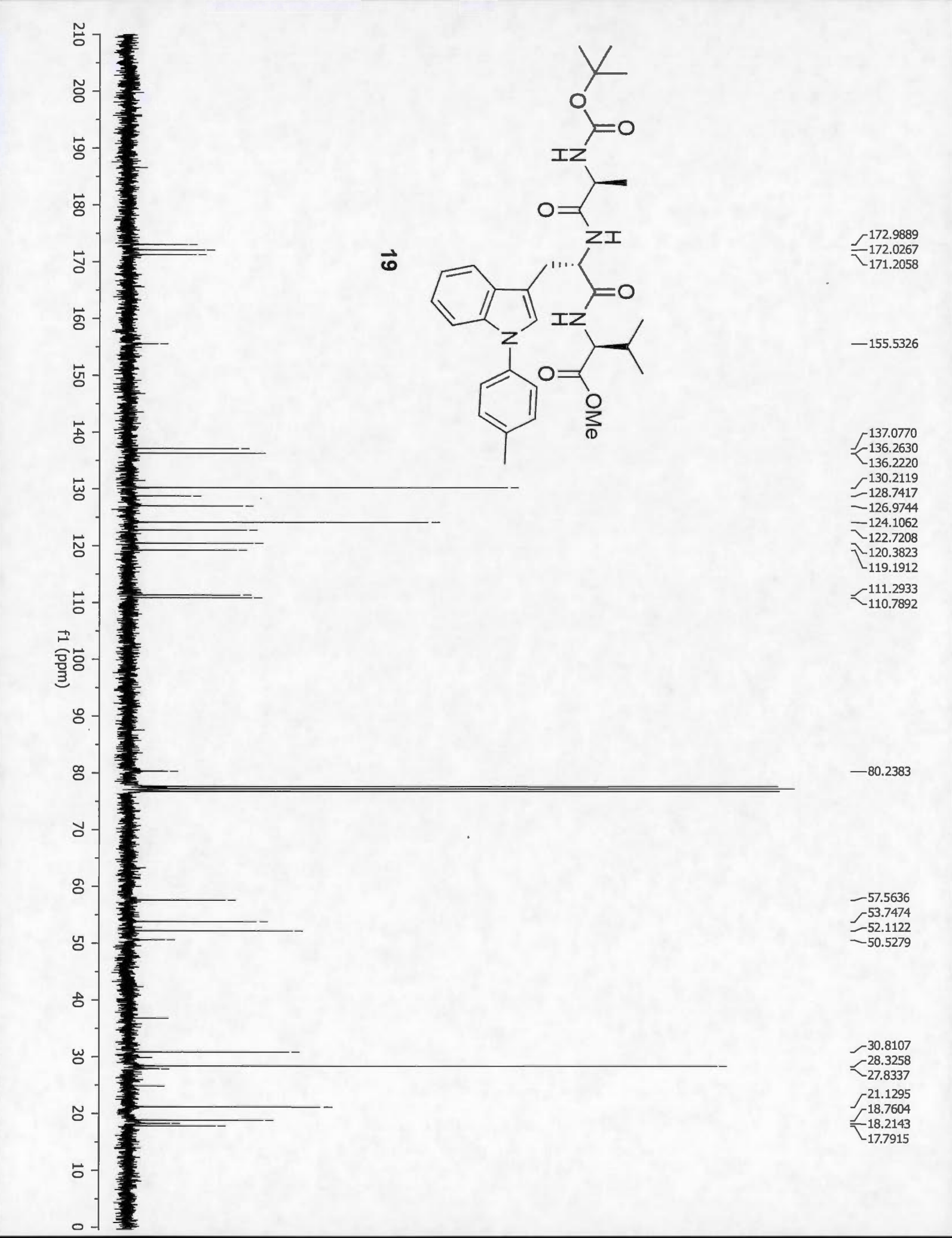
7.5141
7.5091
7.4921
7.4853
7.3581
7.3303
7.2935
7.2603
7.2297
7.2038
7.1929
7.1867
7.1799
7.1680
7.1638
7.1440
6.8477
6.8219
6.5008
6.4779
5.0476
5.0241
4.9324
4.9065
4.8867
4.8606
4.3922
4.3748
4.3641
4.3467
4.0990
4.0196
3.4145
3.3954
3.3662
3.3470
3.2714
3.2450
3.2228
3.1964
2.4144
1.9680
1.9465
1.9269
1.9063
1.3814
1.3091
1.2856
0.6976
0.6719
0.6436
OMe
19
1.07
1.08
2.16
1.95
3.32
1.23
1.00
1.28
1.15
1.13
1.27
2.97
1.19
1.17
3.16
1.77
10.83
3.84
6.26
f1 (ppm)


19
172.9889
172.0267
171.2058
155.5326
137.0770
136.2630
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130.2119
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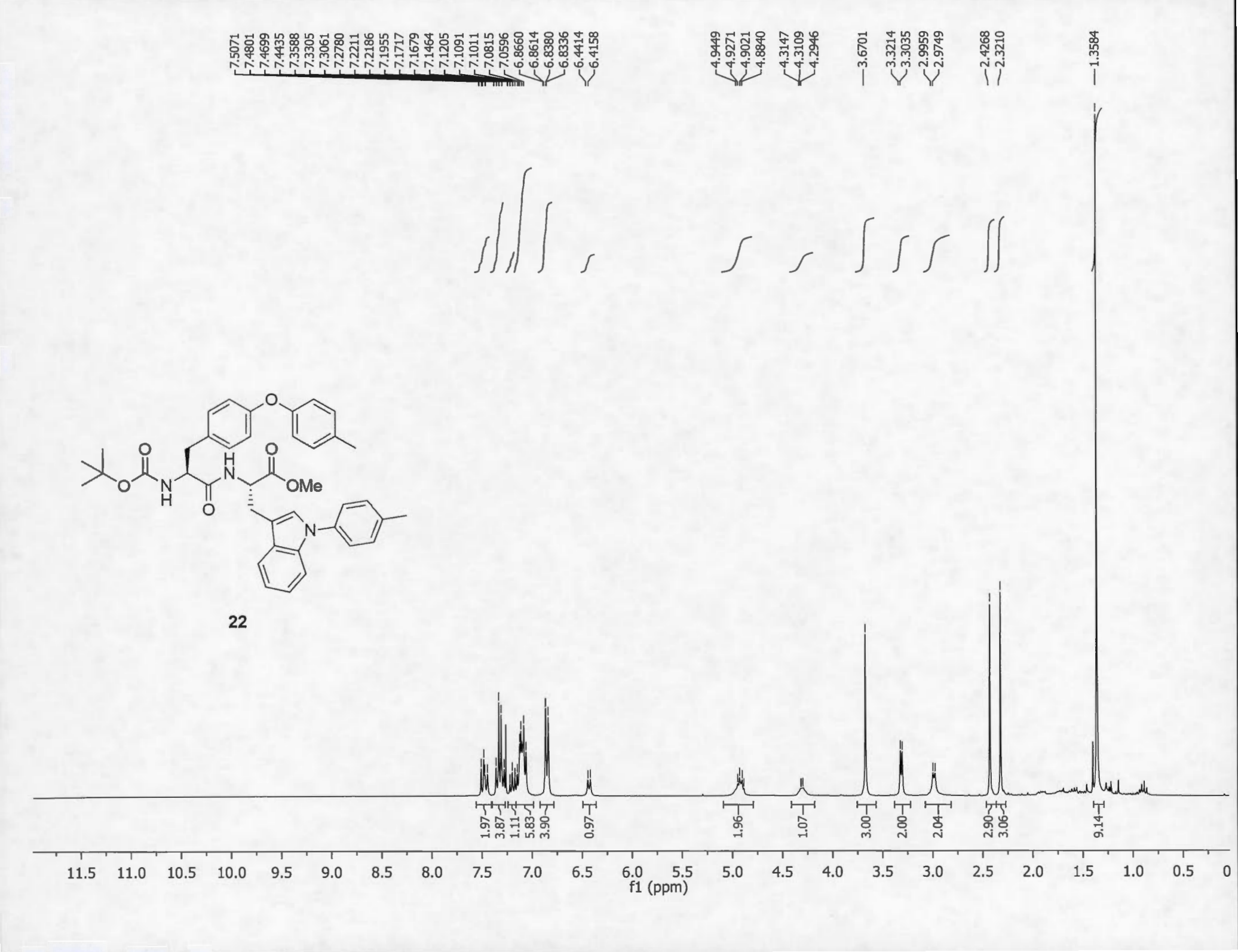
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OMe
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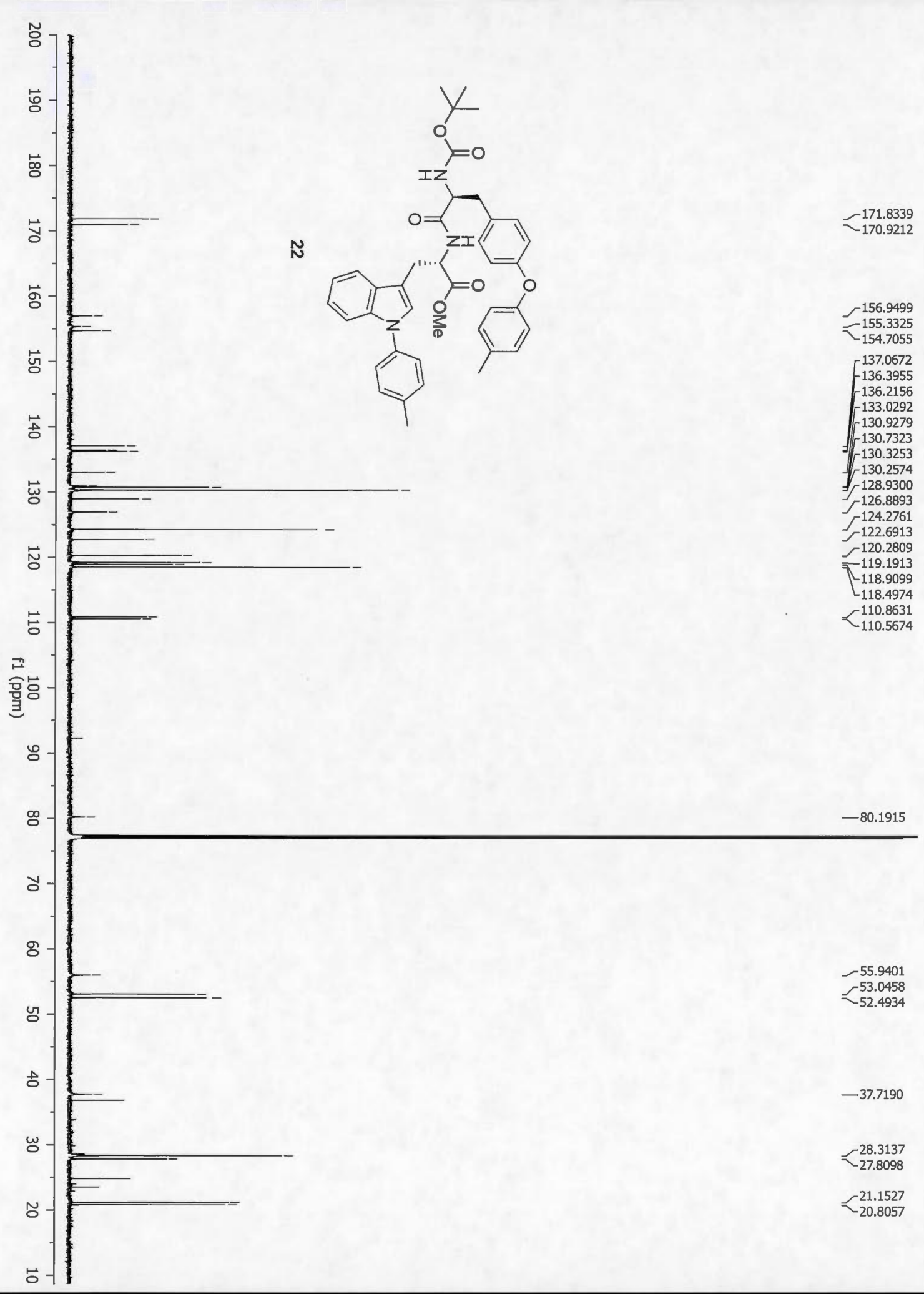
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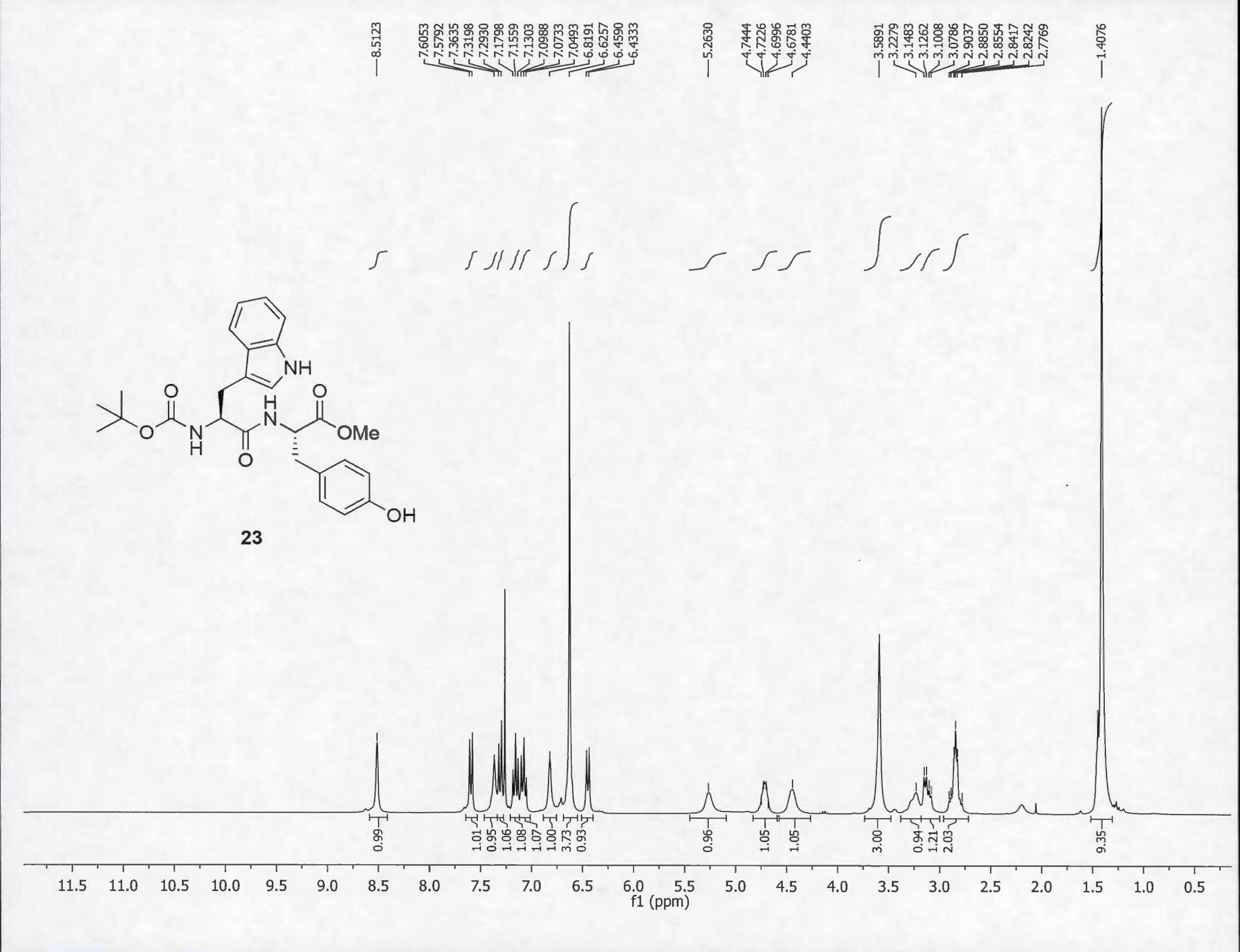
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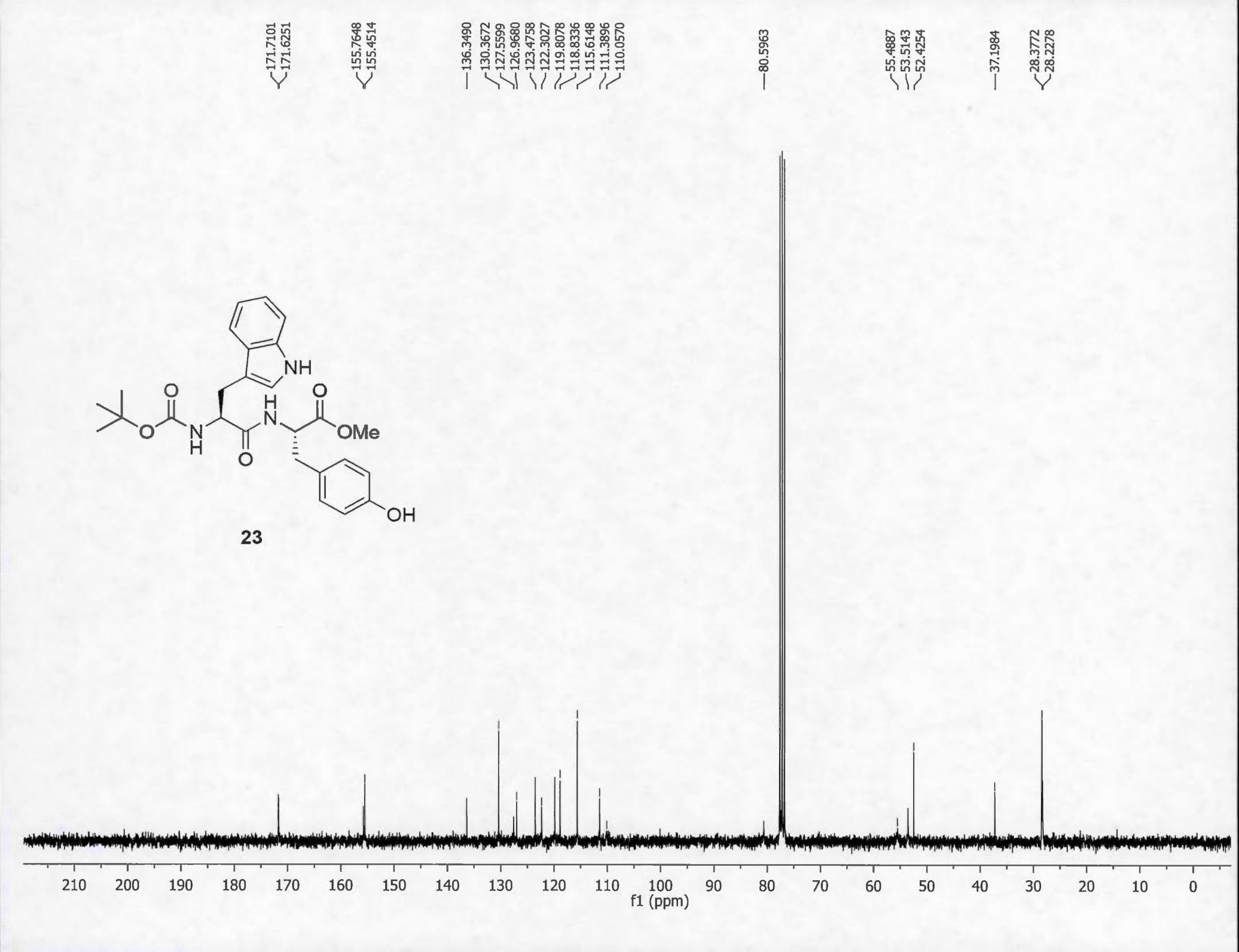
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100
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80
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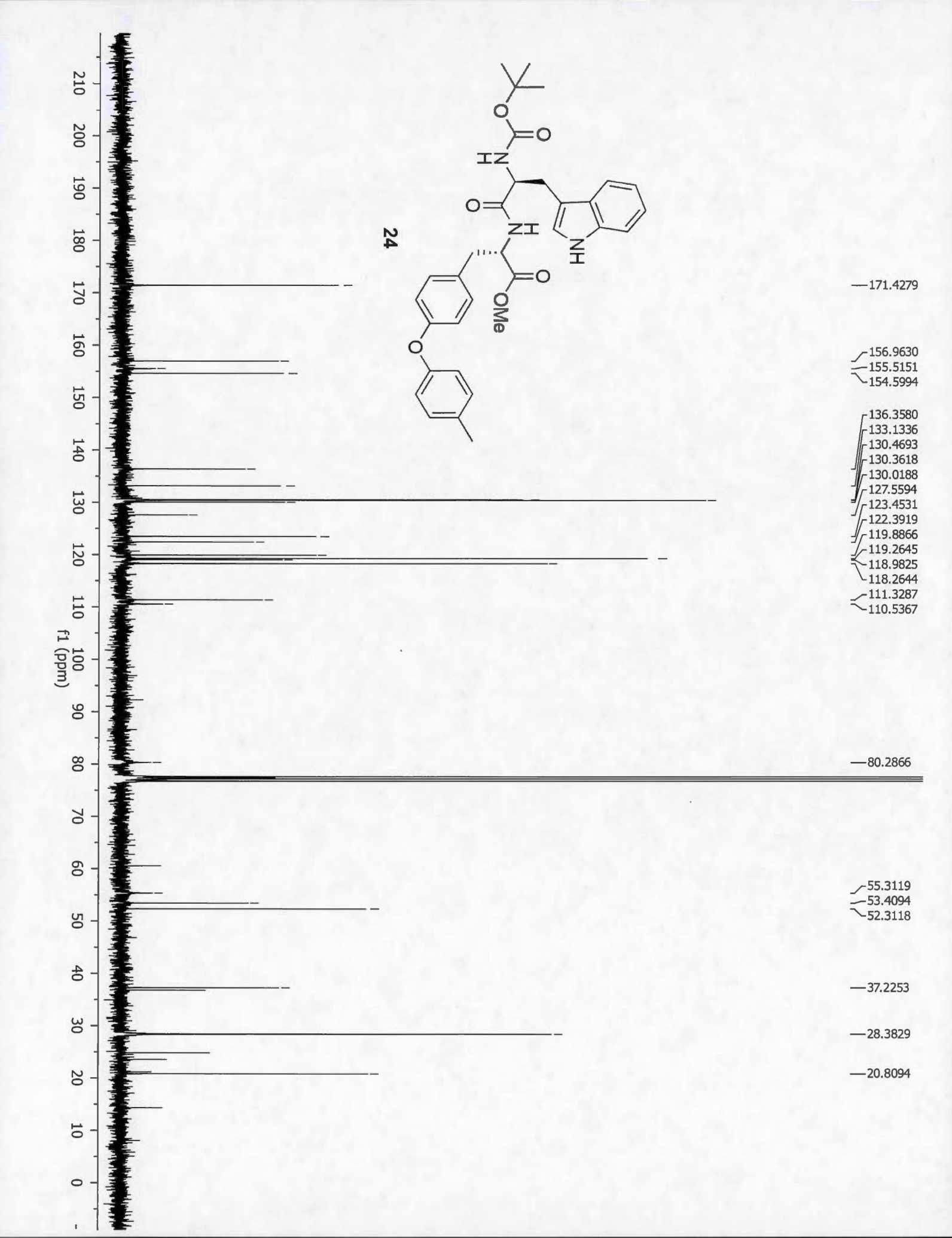
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